MUSCLE RELAXANTS
in Anesthesiology

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MUSCLE RELAXANTS

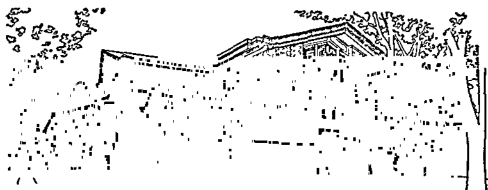
in Anesthesiology

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PREFACE

Good muscular relaxation is an essential requirement for the performance of many surgical procedures. In the past adequate relaxation could only be obtained with deep planes of general anesthesia or by various regional procedures, primarily by subarachnoid block.

Ether and chloroform, the first two agents used for the production of anesthesia, were capable of producing good muscular relaxation without causing undue respiratory depression. In the 1930's first cyclopropane[356,386] and then thiopenthal sodium[262] rapidly became popular anesthetic agents. It soon became evident, however, that with regard to muscular relaxation neither cyclopropane, nor thiopenthal sodium was always capable of fulfilling the requirements of good surgical anesthesia.

While the search continued for new anesthetic agents that would combine the advantages of ether and chloroform on one hand and those of cyclopropane and thiopenthal sodium on the other, more information became available on the pharmacological effects of the anesthetic agents already in use. Chloroform was the first agent to fall victim to the findings of such investigations.[326] In recent years more and more evidence became available that ether, the old standby of anesthesiologists, is by no means harmless under all circumstances. It has been known long that profound changes of intermediary metabolism, such as hyperglycemia and glycopenia, accompany ether anesthesia.[343,268] Various investigators reported that deep ether anesthesia, necessary for produc-

tion of muscular relaxation, can interfere with kidney[63] and liver[8,167] function and decreases myocardial efficiency in laboratory animals.[26,48] Ether may also adversely affect cardiac function in patients with myocardial damage.[140] The unfavorable effect of deep ether anesthesia on circulatory homeostasis has also been demonstrated.[208]

The growing conviction of many anesthesiologists was recently summed up by Gillies[173] who stated, "In many clinics uncompensated depression of respiratory and circulatory functions, seen at its worse in third or fourth plane ether anesthesia and regarded as ideal for abdominal surgery became routine. In submitting to operations involving vital functions directly or indirectly to an extent never before known, patients had enough to overcome on their way to recovery without the extra burden of the metabolic, respiratory and cardiovascular disturbances added by prolonged general anesthesia."

Although subarachnoid block gives excellent muscular relaxation and analgesia with minimal disturbance of the metabolic processes, when it includes the upper thoracic nerves it is frequently accompanied by unwanted circulatory side effects. Furthermore, it does not eliminate the traction reflexes mediated through the vagus that accompany upper abdominal surgery and which usually necessitates the use of heavy supplementation. Another factor responsible for the decreasing popularity of spinal anesthesia has been the emphasis (far out of proportion to their significance) placed in the lay literature on the incidence and severity of neurological complications which occasionally follow its use.

It gradually became evident that the search for a single anesthetic agent, which would ideally fulfill all the requirements of the surgeon, without unduly interfering with the physiological mechanisms of the patient is not

likely to be successful. More and more pharmacologists and anesthesiologists came to believe that ideal operating conditions could be best achieved by the judicious combination of several agents. The goal set was: to utilize the characteristic properties of several agents for the selective depression of certain organic functions, without interfering with vital mechanisms, the depression of which would only endanger the patient, but would not contribute to the requirements of good anesthesia. As early as 1914 Crile[96] advocated the simultaneous use of more than one anesthetic agent. Later Lundy[261a,262a] developed this approach further and coined the term of "balanced anesthesia." It took the foresight of L. H. Wright[185] and the courage and clinical ability of Griffith[186] to introduce curare for the production of muscular relaxation into anesthesiology.

The use of curare in anesthesiology became rapidly popular. Its extensive clinical use and the accompanying experimental studies revealed, however, that the action of curare is not entirely restricted to the neuromuscular junction but that occasionally it effects ganglionic transmission[53] and is responsible for liberation of histamine.[4] These unwanted side effects of curare, which occasionally caused severe fall in blood pressure[187] and bronchiolar spasm,[255] stimulated the search for other compounds with greater selectivity on neuromuscular conduction.

The groundwork for the development of synthetic muscle relaxants was laid by King[244] who isolated d-tubocurarine and determined its structural formula. The pioneering work of Bovet[40] and his associates and the efforts of Barlow and Ing,[19] Paton and Zaimis[302] and many others resulted in the development of a large series of neuromuscular blocking agents, several of which have been used successfully in clinical anesthesia.

AUTHOR'S NOTE

My interest in the use of synthetic muscle relaxants was aroused by Dr. Geoffry Organe of London who in 1949 gave me the first samples of decamethonium. Subsequently, as they became available, other synthetic muscle relaxants were also investigated in the Department of Anesthesia of the Mercy Hospital. All these[141,144,156] fulfilled their main purpose: they produced good muscular relaxation for surgical procedures but all had unwanted side effects and their controllability left much to be desired. Not until we had the opportunity to use succinylcholine in continuous intravenous drip for the production of muscular relaxation[153] did we feel that the goal of the ideal muscle relaxant had been approached as closely as it can be hoped for in the foreseeable future. I felt that the time was ripe for a summing up of the experience gained in more than a decade of clinical and experimental work of numerous investigators with muscle relaxants and started to gather material for a book on the pharmacology and clinical application of neuromuscular blocking agents. In the midst of this work, Dr. John Adriani suggested that I write a monograph on the *Use of Muscle Relaxants in Anesthesiology*. He had little difficulty in convincing me of the urgent need for a practical guide in the use of muscle relaxants and I interrupted my work on the contemplated more extensive treatise to write this monograph, primarily intended for my fellow anesthesiologists.

In accordance with the main purpose of the book the emphasis has been placed on practical considerations

necessary for the safe and efficient administration of muscle relaxants. At the same time I have attempted to include as much of the chemical, physiological and pharmacological aspects of the use of muscle relaxants as is necessary for the understanding of the principles of their clinical application. It is hoped that the first part of the book will also satisfy the needs of medical students and anesthesiologists in training who would like to have easy access to more information on the subject than that available in textbooks of pharmacology. Those who may wish to pursue further certain points are referred to the pertinent bibliographic references. A conscientious effort was made to include in the bibliography as many of the important original publications as feasible within the scope of this little volume. No claim is made for completeness since undoubtedly reference to many excellent papers had to be omitted.

In general instead of proprietary names, generic names have been used. The trade names most familiar to anesthesiologists in the U.S.A. are given when a drug is mentioned the first time. Other trade names are mentioned in the glossary.

To save time for the busy clinician certain terms which might not be familiar to all users of the book are also briefly explained in the glossary. On occasion important practical aspects have been stressed repeatedly in various parts of the book. This has been done partly for quick reference and partly from the point of view of the patient's safety.

ACKNOWLEDGMENTS

I HAVE received help, advice and encouragement from many sources in the course of the clinical and laboratory investigation of muscle relaxants. First of all I would like to thank my present and former clinical associates who cooperated in various phases of the study of muscle relaxants and whose names are mentioned in the pertinent references. Thanks are also due to the members of our laboratory staff who participated in the experimental work. I would like to express my gratitude to the members of the surgical staff of Mercy Hospital, too numerous to be mentioned by name, whose patient cooperation and constructive criticism was of great help. I am especially indebted to Drs. M. Swerdlow, L. Rendell-Baker, S. Thesleff, W. Kalow and D. F. Marsh who gave generously of their time by reading the manuscript at various stages of its preparation, making corrections and giving valuable advice. Drs. P. G. McNall, E. S. Siker, E. G. Erdös, Miss B. V. Dale and Miss N. Baart spent many hours in assembling reprints and verifying references. I want to thank Mrs. Barbara Caputo Leone for devoted secretarial assistance and the typing of the manuscript and Miss Margaret Croup for the excellent illustrations. My thanks are also extended to Drs. E. J. de Beer, D. S. Searle, and W. P. Colvin of Burroughs, Wellcome and Co., Drs. L. O. Randall, R. J. Floody, and L. A. Pirk of Hoffmann-La Roche, Inc., Dr. J. O. Hoppe of Winthrop Stearns Research Inst., Dr. J. M. Ruegsegger of Lederle Laboratories, Dr. F. Prescott of the Wellcome Research Inst. of London, Dr. H. O. J. Collier of

Allan & Hanburys, Ltd., Mr. W. L. Jeffrey of Poulenc (Canada) Ltd. and Mr. T. A. Wilder of May & Baker, Ltd., contributed not only generous supplies of experimental materials but also helpful advice. I also want to thank the numerous investigators who kindly sent me reprints of their publications and frequently permitted me to read their unpublished manuscripts. Finally, I would like to express my indebtedness to Dr. W. D. M. Paton and Madame E. J. Zaimis and the publishers of the *British Journal of Pharmacology* for permission to reproduce Table 5; Dr. J. Gillies and the Royal Society of Medicine for a verbatim quotation, and Dr. W. L. Nastuk and the Editors of the *Journal of Cellular and Comparative Physiology* for their permission to reproduce Figure 2.

The author would be grateful for any papers pertinent to the subject discussed, and for advice on any corrections, omissions, or errors noted in this book.

F. F. F.

CONTENTS

PART TWO: CLINICAL USE

GLOSSARY

acetylcholine esterase enzyme which hydrolyzes acetylcholine to acetic acid and choline.

action potential propagated change in the electrical charge of the endplate region responsible for the initiation of muscular contraction.

afferent pathway sensory pathway leading from the periphery to the central nervous system.

alphaprodine hydrochloride Nisentil.

assisted respiration maintenance of adequate alveolar ventilation through supplementation of the decreased respiratory tidal volume of the patient by manual or mechanical means; respiratory rate and rhythm is controlled by the patient, tidal volume by the anesthetist.

axoplasm the protoplasmic core of the nerve fiber.

benzoquinonium chloride Mytolon, Win 2747.

B. W. 49-204 an antagonist of decamethonium.

B. W. 51-212 an antagonist of succinylcholine.

choline acetylase the enzyme which synthesizes acetic acid and choline to acetylcholine.

cholinergic receptor hypothetical protein molecule with great affinity to acetylcholine, muscle relaxants and certain other quaternary ammonium compounds.

Chondodendron tomentosum plant containing d-tubocurarine.

controlled respiration maintenance of adequate alveolar ventilation by manual or mechanical means in the absence of all discernible respiratory activity of patient; respiratory rate, rhythm and tidal volume are controlled by the anesthetist.

curarines quaternary ammonium bases isolated from "calabash curare."

curines tertiary ammonium bases isolated from "pot" and "tube curare."

decamethonium bromide C10, Syncurine.

depolarization change in the resting potential of membranes caused by a permeability change for sodium and potassium ions.

depolarization block caused by the adsorption of muscle relaxants (e.g., decamethonium) capable of producing prolonged depolarization of the endplate.

DFP Diisopropylfluorophosphate, a cholinesterase inhibitor.

dihydro-β-erythroidine synthetic derivative of β-erythroidine.

dimethyl tubocurarine synthetic dimethyl ether of d-tubocurarine, Metubine, Mecostrin.

edrophonium chloride Tensilon, R02-3198.

efferent pathway leads from the central nervous system towards the peripheral effector organs.

endplate sole plate of Kuhne; modified sarcoplasm.

endplate potential non-propagated change in the electric charge of the endplate.

β-erythroidine alkaloid of Erythrina americana.

eserine physostigmine.

gallamine triethiodide Flaxedil, 2559 F., 3697 R.P.

hexamethonium bromide Bistrium, Hexameton.

hydrolysis the breakdown of an ester to its acid and alcohol constituents.

hypercapnia elevation of the carbon dioxide tension of the blood and tissues; may cause respiratory acidosis.

hypocapnia decreased carbon dioxide tension of the blood and tissues; may cause respiratory alkalosis.

Intocostrin standardized curare extract from Chondendron tomentosum.

laudexium methyl sulphate Laudolissin, Compound 20.

levallorphan tartrate Lorfan, a narcotic antagonist.

lepto-curares muscle relaxants with "thin," elongated molecules.

membrane potential (resting) -90 millivolts, maintained by accumulation of sodium ions on outer surface and that of potassium ions on inner surface of the membranes.

meperidine hydrochloride Pethidine, Demerol.

mixed block a type of neuromuscular block in which a non-

depolarization block is preceded by a depolarization block of short duration.

muscle relaxant neuromuscular blocking agent, myoneural blocking agent.

muscle twitch brief contraction of the muscle fiber; the physiological response to a single nerve stimulus.

muscular contraction the normal response of the mammalian muscle fiber to the stimulation of its motor nerve, or to the rapid intra-arterial injection of acetylcholine; it is a brief shortening of the muscle fiber.

myelin sheath the interior cover of the nerve fiber.

n-allylnormorphine Nalline, Lethidrone a narcotic antagonist.

neostigmine methylsulphate Prostigmine.

neurilemma sheath of Schwann, outside cover of nerve fiber.

neuromuscular junction myoneural junction, myoneural synapse, synapse.

neuromuscular transmission propagation of the nerve impulse through the myoneural junction to the muscle fiber.

non-depolarization block "competitive" block of Paton; caused by the adsorption of non-depolarizing muscle relaxants (e.g., curare) to the cholinergic receptors of the endplate.

overshoot terminal phase of the depolarization process during which the endplate becomes electropositive.

pachy-curares muscle relaxants with "thick" round molecules.

parasympatholytic drugs drugs which antagonize the peripheral effects of parasympathetic stimulation; atropine or scopolamine.

pentobarbital sodium Nembutal.

phenobarbital sodium Luminal.

postjunctional membrane functional membrane covering the sole plate; distal boundary of the subneural space.

protocurines quaternary ammonium bases isolated from "pot curare."

quaternary ammonium group a radical containing positively charged nitrogen atom with five chemical valences.

rabbit head-drop test method used for the biological assay of muscle relaxants.

"red muscle" darker than "white muscle"; contracts slowly; can be tetanized at relatively slow rates of stimulation; more sensitive to d-tubocurarine than to decamethonium.

repolarization restitution of the resting membrane potential of the endplate to its original value of -90 millivolts.

sarcolemma membranous cover of the muscle fiber.

sarcoplasm protoplasm of muscle fiber.

stilbamidine tertiary nitrogen compound with neuromuscular activity.

storage protein a hypothetical protein that keeps acetylcholine in inactive bondage.

subneural space microscopic gap between the terminal membrane and the sole plate.

succinyldicholine succinylcholine, suxamethonium, diacetylcholin, succinoylcholine, Anectine, Scoline, Brevidil "M," Celocurine.

suxethonium Brevidil "E."

sympathetic hyper-reactor patient with an increased irritability and reactivity of the sympathetic nervous system.

tachyphylaxis decreased pharmacological response to the same dose on repeated administration.

TEPP tetraethylpyrophosphate, a cholinesterase inhibitor.

terminal membrane the membranous termination of the axoplams at the myoneural junction; the proximal boundary of the subneural space.

tetanus the sustained contraction of the muscle fiber caused by repetitive stimulation at short intervals (less than 50 milliseconds).

thiopental sodium thiopentone, Pentothal.

toxiferine-I alkaloid of Strychnos toxifera, ingredient of "calabash curare."

Tubadil a depository d-tubocurarine preparation.

tubocurarines quaternary ammonium bases isolated from "tube curare."

d-tubocurarine alkaloid from Chondodendron tomentosum.

white muscle lighter than "red muscle"; contracts rapidly; can be tetanized with relatively high rates only; more sensitive to decamethonium than to d-tubocurarine.

MUSCLE RELAXANTS
in Anesthesiology

PART ONE

Basic Considerations

1

THE HISTORY OF MUSCLE RELAXANTS

Early history. Botanical identification. Early experimental work. Physiology of neuromuscular transmission. Early attempts at clinical application. Introduction of curare into anesthesiology. Development of synthetic muscle relaxants.

THE history of muscle relaxants has its beginning in the sixteenth century. This fascinating subject is masterfully discussed in two excellent monographs by McIntyre[277] and Granier-Doyeux.[181] Most of the data relating to the outstanding events in the history of curare to be discussed in this chapter have been obtained from these publications.

Sir Walter Raleigh in his *Discovery of Guiana,*[312] published in 1595, mentions the arrow poison of the Indians. The first eyewitness account of the preparation of curare was by Humboldt[225] who suspected that curare was prepared from various plants of the Strychnos family by natives of British Guiana. Schomburgk[340] later verified his assumption.

The botanical identification of the sources of the various curares, and the analysis of their active ingredients has never been carried out satisfactorily. Some semblance of order was made in this chaotic complex by Boehm[35] who distinguished, depending on the container in which they were available, tube, pot, and calabash curare; but

many years were to pass before a more scientific classification became possible.

Early experimental work with curare dates back to the eighteenth century. A variety of animals were used in these experiments, the detailed description of these can be found in McIntyre's[277] monograph. At about the same time that Brodie[50,51] showed that fully curarized animals could be kept alive by artificial respiration, Humboldt and Bonpland[226] carried out the first curare experiments with frog nerve-muscle preparations. The earliest scientifically planned investigations on the neuro-muscular activity of curare were done by Claude Bernard in 1850.[28] He showed that the injection of curare into the lymph sac of frogs paralyzed the animals although the conductivity of the nerves and the irritability of the muscles to direct stimulation remained unchanged.[29]

The isolation of d-tubocurarine from tube curare by King in 1935[244] gave renewed impetus to the investigation of the mode of action of neuromuscular blocking agents. It was followed rapidly by a number of important steps in the development of the pharmacology and clinical application of muscle relaxants. Thus Dale and his coworkers[102] showed that the stimulation of motor nerves was accompanied by acetylcholine release at the neuromuscular junction. Cowan[93] demonstrated that the acetylcholine released depolarized the endplate and the current produced by this depolarization, later termed *endplate potential by Eccles and his coworkers,*[123] was responsible for the initiation of muscular contraction. Subsequently Eccles and his colleagues[124] showed that the anti-curare activity of eserine, first described by Pal in 1900,[296] depends on its anticholinesterase activity. In the following decade neuromuscular transmission was the subject of lively debate between exponents of the elec-

trical and chemical transmission theories. It is now almost universally accepted that both physico-chemical processes centering around the role of acetylcholine and electrical phenomena are essential for neuromuscular transmission.[406] Much of the work on the physiology of neuromuscular transmission was done with the help of muscle relaxants. Thanks to the work of Burns and his coworkers,[63] Burns and Paton,[64] Paton and Zaimis[305] and others, considerable information became available on the mechanism of action of the various neuromuscular blocking agents.

While the exposition of the physiology of neuromuscular transmission and the pharmacology of neuromuscular blocking agents was progressing, the clinical use of muscle relaxants became more and more widespread. Sporadic attempts at the clinical application of various curare preparation date back to the middle of the nineteenth century. The early pioneers of the modern therapeutic application of curare were Bremer and his coworkers[46,47] and Hartridge and West.[202,203]

Real progress in the clinical application of curare was made possible by the cooperation of several investigators. McIntyre and his associates at the University of Nebraska together with the research staff of I. R. Squibb and Sons prepared first a purified curare extract from crude curare brought to the United States by Gill.[172] This preparation, on the suggestion of McIntyre, was used by Bennett in 1938 for the prevention of trauma in electroshock therapy.[23,25] Subsequently Intocostrin, a curare extract standardized by the ingenious rabbit head-drop test of Holaday,[215,380] was obtained from a single plant, Chondodendron tomentosum. Later Wintersteiner and Dutcher[408] prepared crystalline d-tubocurarine from the same plant.

Curare was first used in anesthesia by Griffith and

Johnson,[186] who at the suggestion of L. H. Wright, administered it in the form of Intocostrin to anesthetized patients. Soon thereafter Cullen[98,99] published his experiences with the first large series of cases in which curare was used for the production of muscular relaxation in anesthetized patients.

Partly because of the relatively difficult access to Chondodendron tomentosum, and partly because of the incidence of unwanted side effects[187,255] that occasionally accompanied the use of d-tubocurarine, a systematic search was started by several independent groups of investigators for synthetic compounds with more selective action on the neuromuscular junction. In 1946 Bovet and his associates[41] synthetized 3381RP. The neuromuscular activity of this compound was comparable to that of d-tubocurarine. In the following year Bovet and his coworkers[42] described the synthesis and the pharmacological properties of gallamine triethiodide (Flaxedil) (see formula on p. 16), an agent which since has been used extensively in anesthesiology. Shortly afterwards, Barlow and Ing[19] and Paton and Zaimis[302] simultaneously, but independently, reported on the neuromuscular activity of decamethonium (Syncurine). At about the same time Collier[86] described the pharmacological properties of the dimethyl ether of d-tubocurarine previously prepared by King[244] and Dutcher[121]. Benzoquinonium chloride, (Mytolon) another compound that also has been used clinically, was synthetized by Cavallito *et al.*[74] and studied by Hoppe.[218]

The synthetic compound succinyldicholine which approaches most closely the ideal muscle relaxant,[151] has been lying idly on the shelves of chemists since it was first prepared by Hunt in 1906.[228] In 1949 Bovet and his associates[43] and Phillips[308] independently discovered the

neuromuscular activity of this compound. After extensive pharmacological investigations by Bovet *et al.*,[43] Bovet-Nitti,[45] Castillo and de Beer,[72] Ginzel *et al.*,[175,176,177] Thesleff[365,366,367] and many others, it was introduced into clinical practice in Austria by Brücke *et al.*[58] and Mayrhofer and Hassfurther,[276] in Sweden by Dardel and Thesleff,[104,105] in England by Scurr[341] and Bourne *et al.*,[88] and in the United States by Foldes *et al.*[153]

The search for the ideal muscle relaxant can by no means be considered concluded. In recent years numerous agents have been synthetized. Some of these for example, suxethonium[378] (Brevedil "E") and laudexium[34] (Laudolissin) have been used clinically, the investigation of many other compounds, however, have been abandoned at the laboratory stage.

2

CHEMISTRY OF MUSCLE RELAXANTS

Naturally occurring muscle relaxants. Synthetic muscle relaxants.

A LARGE number of naturally occurring and synthetic compounds are capable of inhibiting neuromuscular transmission. The chemistry of most of these compounds known before 1948 was summarized by Craig[95] and much of the recent work on the chemistry of synthetic neuromuscular blocking agents was reviewed by Bovet[40] and Barlow.[18]

Though the clinically used muscle relaxants discussed in the present monograph all contain at least two quaternary ammonium groups, the presence of this radical is not indispensable for neuromuscular blocking activity. In the following paragraphs the neuromuscular blocking agents will be arbitrarily divided into: a) naturally occurring alkaloids and their derivatives, and b) synthetic compounds. A further subdivision will be made based on the presence or absence of quaternary ammonium groups (see Table 1).

NATURALLY OCCURRING MUSCLE RELAXANTS

Most naturally occurring neuromuscular blocking agents have been isolated from crude curare preparations. The main ingredient of the various curares made by the Indians of South America was either the bark of one of

TABLE 1

THE CLASSIFICATION OF MUSCLE RELAXANTS

A. *Naturally Occurring Alkaloids and Their Derivatives**

Compound	*Source*	*Characteristic Groups*
Curarines	Calabash Curare	2 Quaternary Nitrogen
Protocurines	Pot Curare	2 Quaternary Nitrogen
d-Tubocurarine	Tube Curare Chondodendron Tomentosum	2 Quaternary Nitrogen
Dimethyl Tubocurarine	Synthetic	2 Quaternary Nitrogen 2 Methyl Ether
Toxiferins	Calabash Curare Strychnos Toxifera	1 Quaternary Nitrogen
Curines	Tube Curare	2 Tertiary Nitrogen
β-Erythroidine	Erythrina Americana	1 Tertiary Nitrogen
Dihydro β-Erythroidine	Synthetic	1 Tertiary Nitrogen

B. *Synthetic Muscle Relaxants***

*Non-depolarizing****	*Depolarizing****
Gallamine Triethiodide	Decamethonium Chloride
Benzoquinonium Chloride	Succinylcholine Chloride
Laudexium Methylsulphate	Suxethonium Bromide

* All naturally occurring alkaloids are non-depolarizing muscle relaxants.
** All synthetic muscle relaxants contain quaternary nitrogens.
*** Based on their activity in man.

the many varieties of the genus Strychnos, most frequently Strychnos toxifera, or the vines of Chondodendron tomentosum.[272]

Although Boussingault and Roulin[327] prepared an extract from curare in 1827, the first systematic approach to the problem of the isolation of curare alkaloids was made by Boehm.[35] He isolated quaternary ammonium bases called curarines from the three available varieties of crude curare. According to the source of their origin he named the products obtained from calabash curare,

curarines, those extracted from pot curare protocurines and the extracts of tube curare, tubocurarines. He also isolated from pot and tube curare tertiary bases with weak neuromuscular activity which he termed curines.

The chemistry of tube and pot curare was later investigated by King.[244] In 1938 McIntyre obtained the first standardized curare preparation from Chondodendron tomentosum. Subsequently Wintersteiner and Dutcher[408] prepared from the same plant crystalline d-tubocurarine which was previously isolated from tube curare by King in 1935.[244] A clinically employed ether derivative of d-tubocurarine, dimethyl tubocurarine was also prepared by King[244] and by Wintersteiner and Dutcher.[408]

Calabash curare was studied by Wieland and his *associates;*[397,398,399,400] *by Karrer and Schmid,*[238,336–339] Waser,[383,384] and by Marsh.[272] Of the numerous alkaloids isolated from calabash curare, the most interesting is toxiferine-I which although it is perhaps the most potent of all neuromuscular blocking agents, contains only one quaternary ammonium group. Toxiferine-I was also isolated from the bark of Strychnos toxifera by King[245] and studied by Paton and Perry[301] who found that this compound showed the least species variation of all the neuromuscular blocking agents investigated.

Another naturally occurring alkaloid with neuromuscular blocking activity is β-erythroidine isolated from the Erythrina americana by Folkers and Major.[161] This compound, in contrast to the curare alkaloids, is a tertiary amino derivative and contains no quaternary ammonium groups. Dihydro-β-erythroidine later prepared from the mother compound by Folkers and Major[162] also has neuromuscular blocking activity. Quaternary derivatives of naturally occurring cinchona, pyridine, isoquinoline, and

tropine alkaloids are also capable of interrupting neuromuscular transmission.[95]

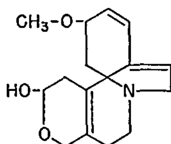
SYNTHETIC MUSCLE RELAXANTS

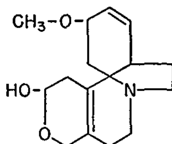
The relationship between the quaternary ammonium groups of curare and its neuromuscular activity was already recognized by Crum-Brown and Fraser in 1869.[97] It has subsequently been shown that other onium salts are also capable of inhibiting neuromuscular transmission[95] and that tertiary ammonium compounds like stilbamidine[27] have similar properties.

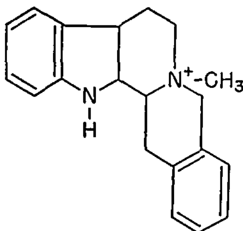
The first attempts at the production of synthetic muscle relaxants was the synthesis of quaternary methylstrychnine and methylbrucine derivatives by Crum-Brown and Fraser.[97] More recent efforts in this direction center around the importance of optimally placed quaternary ammonium groups.[19,20] The optimal distance between these groups was estimated to be about 13 to 15 Å.[243] The muscle relaxants used most frequently in clinical practice all contain two or more quaternary ammonium groups. These groups, whether separated by a straight chain as in decamethonium or succinylcholine, or by aromatic radicals, as in benzoquinonium, gallamine, or laudexium, are about 15 Å from one another.

Some of the physical and chemical properties of the muscle relaxants in clinical use or of special theoretical interest are summarized in Table 2. The structural formulas of the same compounds are shown in Figure 1. Here the discussion will be limited to the correlation between certain changes in the molecule of neuromuscular blocking agents and their activity.

In general, converting a tertiary nitrogen compound into a quaternary one will increase neuromuscular activity.[95,219] Substitution of the methyl radicals in the



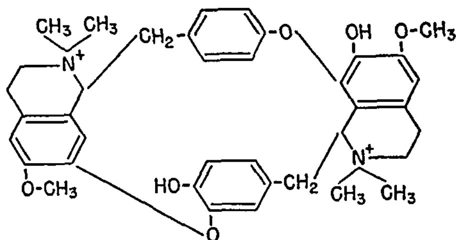




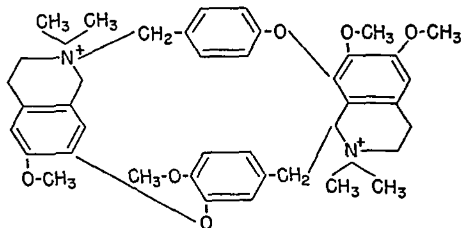
C-TOXIFERIN I

$C_{20}H_{23}N_2O$

Figure 1a. The structural formulae of C-toxiferin I, β-erythroidine and dihydro-β-erythroidine.

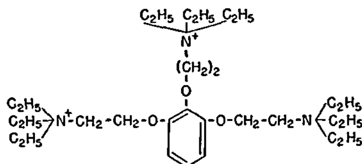


D-TUBOCURARINE
$C_{38}H_{44}N_2O_6$

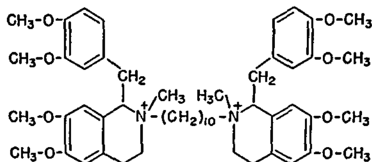


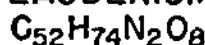
DIMETHYL TUBOCURARINE
$C_{40}H_{48}N_2O_6$

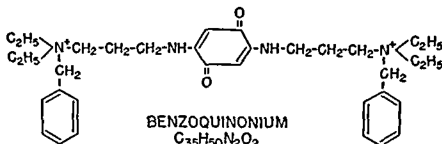
Figure 1b. The structural formulae of d-tubocurarine and dimethyl tubocurarine.











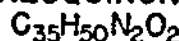
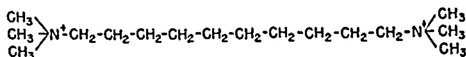
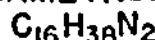
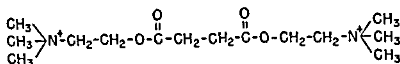
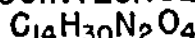


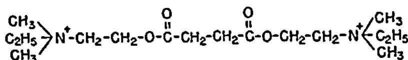
Figure 1c. The structural formulae of gallamine, laudexium and benzoquinonium.











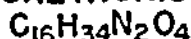


Figure 1d. The structural formulae of decamethonium, suxamethonium and suxethonium.

quaternary ammonium groups with ethyl radicals[177,221] or with nitrobenzyl radicals[315] changes certain depolarizing muscle relaxants to non-depolarizing agents. Increasing or decreasing the distance between the quaternary nitrogen groups cause similar changes in the activity of depolarizing muscle relaxants. For example, tridecamethonium in contrast to decamethonium produces an antidepolarizing block.[414]

This brief description of the chemistry of muscle re-

TABLE 2

PHYSICAL AND CHEMICAL PROPERTIES OF MUSCLE RELAXANTS

Compound	*Chemical Formula of Cation*	*Molecular Weight of Cation*	*Available Salts*	*Melting Point °C*	*Color*	*Solubility in Water*	*Miscibility with Barbiturates*	*Stability*
A. TERTIARY AMMONIUM DERIVATIVES:								
β-Erythroidine	$C_{16}H_{19}NO_3$	275 0	HCl	232	white	good	good	cannot be autoclaved
Dihydro-β-erythroidine	$C_{16}H_{21}NO_3$	277.0	HBr	241	white	good	good	cannot be autoclaved
B. QUATERNARY AMMONIUM DERIVATIVES:								
a. Mono-quaternary compounds:								
C-toxiferine-I	$C_{20}H_{23}ON_2$	307.4	Chloride	—	red	good	good	good
b. Bis-quaternary compounds:			Picrate	265	yellow	good	good	good
d-Tubocurarine	$C_{38}H_{44}O_6N_2$	624.7	Chloride	268–269	white	good	not readily miscible	can be autoclaved
Dimethyl tubocurarine	$C_{40}H_{48}O_6N_2$	652.8	Chloride and Iodide	236 267–270	white	good	miscible	can be autoclaved
Benzoquinonium	$C_{34}H_{50}O_2N_4$	617.7	Chloride	191–194	red	good	miscible	can be autoclaved
Laudexium	$C_{52}H_{74}N_2O_8$	851.1	Methyl-sulfate	—	white	good	not miscible	good
Decamethonium	$C_{16}H_{38}N_2$	330 6	Bromide	252	white	good	miscible	can be autoclaved
Succinylcholine	$C_{14}H_{30}O_4N_2$	290.4	Chloride and Bromide	160–164 225	white	good	miscible decomposes rapidly	can be autoclaved
Surethonium	$C_{16}H_{34}O_4N_2$	318.4	Bromide	158	white	good	miscible decomposes rapidly	decomposes slowly on standing
c. Tri-quaternary compounds:								
Gallamine	$C_{30}H_{60}O_3N_3$	510 9	Iodide	250	white	good	miscible	can be autoclaved

laxants could only cover some of the salient points of recent developments. Even so, the progress made in the elucidation of the relationship between chemical structure and pharmacological activity of these compounds is evident.[10,18] It should be gratifying to those active in this field of endeavor that their approach to the solution of this important problem will undoubtedly serve as a model for the clarification of similar problems in other realms of pharmacological investigation.

3

PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION

Structure of the neuromuscular junction. Mechanism of neuromuscular transmission. Actions of acetylcholine at the endplate: acetylcholine contraction; acetylcholine contracture; acetylcholine depression.

STRUCTURE OF THE NEUROMUSCULAR JUNCTION

OUR knowledge of the synapse between the motor nerve ending and the muscle fiber, called the neuromuscular junction or myoneural junction, is based mainly on the work of Kuhne,[250a] Couteaux[91,92] and Carey[70,71] and can be briefly summarized as follows:

After the motor nerve fiber penetrates the sarcolemma of the muscle fiber it loses its myelin sheath and the neurilemma blends with the sarcolemma. The axoplasm spreads out in close contact with the sarcolemma and it is assumed that the side facing the muscle fiber is covered by the terminal membrane. The terminal membrane is separated by a microscopic gap, the subneural space, from the sole plate of Kuhne. Morphologically the sole plate is modified sarcoplasm of the muscle fiber. The side of the sole plate facing the terminal membrane is covered by the post-synaptic or post-junctional membrane. The subneural space is therefore limited on one side by the ter-

minal membrane of the motor nerve ending and on the other by the post-junctional membrane.

MECHANISM OF NEUROMUSCULAR TRANSMISSION

Despite the intensive research of the last two decades certain aspects of neuromuscular transmission are still controversial. It has now been generally accepted that both electrical phenomena and the acetylcholine-acetylcholine esterase system play important roles in neuromuscular transmission.[188] It seems that the difference between the exponents of the "chemico-electrical" theory of Feldberg (see Grundfest)[190] and Nachmansohn's "electro-chemical" theory[289] is mainly one of emphasis. The former claims that the depolarization of the endplate is caused by the acetylcholine secreted at the terminal membrane that diffuses through the subneural space to reach the post-junctional membrane. In contrast to this, Nachmansohn claims that the current generated at the terminal membrane jumps the few micron-wide gap, presented by the subneural space. The electrical current liberates acetylcholine at the post-junctional membrane and is responsible for the depolarization of the endplate.

The essentials of neuromuscular transmission, which according to Nachmansohn are basically not different from axonal conduction[406] can be summarized as follows:

The post-junctional membrane like the nerve axon, contains acetylcholine, four different types of proteins associated with acetylcholine metabolism and various ions. The resting post-junctional membrane is polarized (see Figure 2). The interior of the post-junctional membrane is rich in potassium ion, poor in sodium ion and is electronegative with reference to the outer surface which is rich in sodium and poor in potassium.

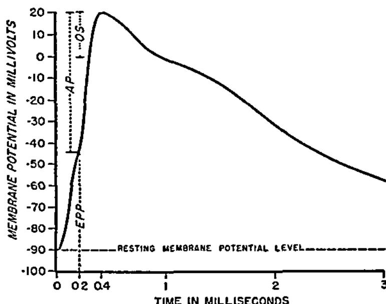


Figure 2. E P P endplate potential; A P action potential; O S overshoot. Due to the release of acetylcholine by the nerve impulse at the endplate at zero time the endplate potential is generated and in about 0.2 milliseconds the resting membrane potential of the endplate (—90 millivolt) decreases to —45 millivolts. When this critical level is reached the potential change, from here on termed action potential, becomes propagated, within another 0.2 milliseconds overshoots and becomes electro-positive (+15—20 millivolts). Within the next 2 to 3 milliseconds the endplate becomes

The electrostatic difference between the outer surface and the interior of the resting endplate is about −90 millivolts.[201] This −90 millivolts is called the resting membrane potential and is to be clearly distinguished from the "endplate potential" to be described.

In the resting post-junctional membrane acetylcholine is bound in an inactive form to one of the above mentioned four proteins. When the nerve impulse reaches the myoneural junction, acetylcholine is liberated from its protein bondage. The liberated acetylcholine is adsorbed immediately to the second protein, which is also known as the cholinergic receptor of the endplate. Due to the adsorption of acetylcholine to it, the cholinergic receptor changes its configuration and thereby increases the permeability of the post-junctional membrane for sodium and potassium ions. Due to this temporary increase in permeability, potassium diffuses out of, and sodium diffuses into the endplate and the potential difference between the interior and the exterior of this structure rapidly decreases (see Figure 3). This rapid change in the negativity of the resting membrane potential of the endplate was termed by Eccles[123] the "end plate potential." This potential is a monophasic non-propagated change in the electrical charge of the endplate which in about 0.3 milliseconds[201] decreases the potential difference between the inside and the outside of the endplate to about half of its original value (−45 millivolts). As long as the magnitude of the endplate potential does not exceed 45 millivolts, it does not spread to other parts of the muscle fiber, and there is no muscular contraction. When, however, in the course of the depolarization process this critical membrane potential (−45 millivolts) is surpassed, the speed of the depolarization process increases and the potential becomes propagated. From this point on the endplate po-

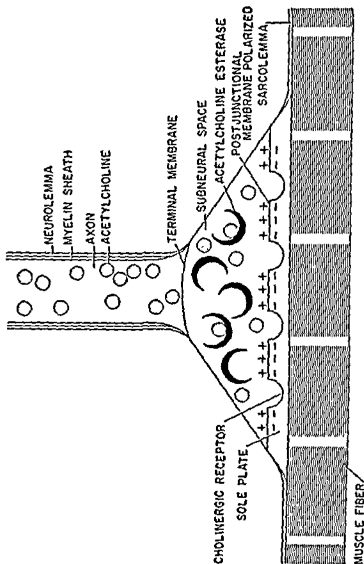


Figure 3. Schematic representation of the resting endplate. Note that the postjunctional membrane is polarized.

tential as such cannot be distinguished and the potential change is termed action potential. Within another 0.2 milliseconds the negative membrane potential of the endplate, and that of the adjacent muscle membrane, not only decreases to zero but becomes electro-positive by 15 to 20 millivolts relative to the outside.[201] This phenomenon is termed overshoot. Because of its fusion with the action potential the endplate potential can only be recorded if the development of the action potential is prevented by partial curarization.[122]

The endplate, however, remains depolarized for only 2–3 milliseconds because shortly after its adsorption to the cholinergic receptors, acetylcholine is attracted to the third protein, the acetylcholine esterase, present in the post-junctional membrane and is rapidly hydrolyzed to acetic acid and choline. Simultaneously the post-junctional membrane becomes repolarized and the membrane potential of the endplate returns to its resting level of −90 millivolts. Due to a time lag of 2 to 3 milliseconds between the development of the action potential and the start of muscular contraction the beginning of the muscle twitch coincides approximately with the end phase of the repolarization process (see Figures 4 and 5). Subsequently the hydrolysis products of acetylcholine, choline and acetic acid, are resynthetized by the fourth protein, called choline acetylase, to acetylcholine which is adsorbed to the storage protein thereby completing the cycle. It is evident from the foregoing that normal myoneural transmission depends on this depolarization-repolarization sequence, and anything that will interfere with either the depolarization or the repolarization of the endplate will inhibit neuromuscular transmission.[151] The events that accompany normal neuromuscular transmission are summarized in Table 3, and the changes in the state of

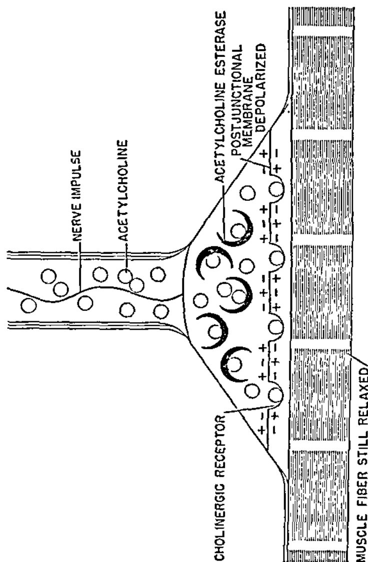


Figure 4. The effect of nerve impulse on the endplate. Note: a) the increased acetylcholine concentration at the endplate; b) cholinergic receptors are occupied by acetylcholine; c) postjunctional membrane is depolarized. Muscle fiber is still relaxed.

TABLE 3

SUMMARY OF EVENTS THAT ACCOMPANY NEUROMUSCULAR TRANSMISSION

Nerve impulse liberates acetylcholine at the endplate.
Acetylcholine is adsorbed to cholinergic receptors.
Endplate becomes depolarized; endplate potential is generated.
Endplate potential reaches a critical level; action potential is initiated.
Acetylcholine is hydrolyzed by acetylcholine esterase to acetic acid and choline.
Endplate becomes repolarized.
Muscular contraction occurs towards end of repolarization phase.
Acetic acid and choline are resynthetized by choline acetylase to acetylcholine.

polarization and in the membrane potential of the endplate in relation to the contraction of the muscle fiber are schematically presented in Figure 6.

THE ACTIONS OF ACETYLCHOLINE AT THE MOTOR ENDPLATE

According to Feldberg[138] acetylcholine, depending on the species investigated and on the experimental circumstances, can produce, through its action at the neuromuscular junction contraction or contracture of the muscle fiber or inhibition of neuromuscular transmission. The various effects of acetylcholine at the neuromuscular junction were recently discussed in an excellent monograph by Riker.[322] Under suitable experimental conditions, the depolarizing muscle relaxants, to be discussed later, can imitate both the depressant and the stimulating properties of acetylcholine.[303,176]

ACETYLCHOLINE CONTRACTION

In mammals the physiological response to the action of acetylcholine at the neuromuscular junction is muscular contraction. This muscular contraction can be elicited by the acetylcholine liberated at the neuromuscular junction

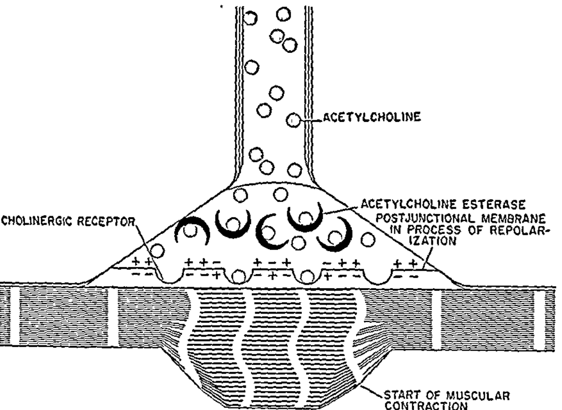


Figure 5. 2.5 to 3.0 milliseconds later than in Figure 4. Postjunctional membrane almost completely repolarized, muscle fiber just starting to contract.

by the nerve impulse, or by the close intra-arterial injection of small quantities (as little as 2 microgm) of acetylcholine.[52,57] In the normal mammalian muscle a single nerve impulse or the intra-arterial injection of a small amount of acetylcholine will result in a single muscle twitch. The muscle twitch follows the depolarization of the endplate by 2 to 3 milliseconds, and its duration is about 100 milliseconds. This is so because acetylcholine is hydrolyzed by the acetylcholine esterase present at the neuromuscular junction, and by the time the muscle fiber recovers from its refractory phase the endplate is no longer depolarized, there is no endplate potential and consequently no repeated contraction of the muscle fiber. When the concentration of acetylcholine is maintained for a longer period at the endplate either by the use of anticholinesterases (e.g., eserine), or by the intra-arterial injection of acetylcholine, a single nerve impulse can elicit several twitches, or a short tetanus. The sensitivity of the chronically denervated mammalian muscle to acetylcholine is markedly increased.[166,101,171,52]

In amphibian and avian muscle, depending on its type of innervation, acetylcholine can cause either contraction or sustained contracture. The frog-rectus, which has a nerve supply composed of small caliber fibers, responds to acetylcholine with sustained contracture.[249,250,227] In contrast to this the frog sartorius innervated by large caliber fibers, responds to acetylcholine by a single contraction. Response of avian muscle to acetylcholine resembles that of the amphibian or denervated mammalian muscle, rather than that of the normal mammalian muscle.[54]

ACETYLCHOLINE CONTRACTURE

As already mentioned, the physiological response to acetylcholine in certain amphibian[321] and avian[54] muscles

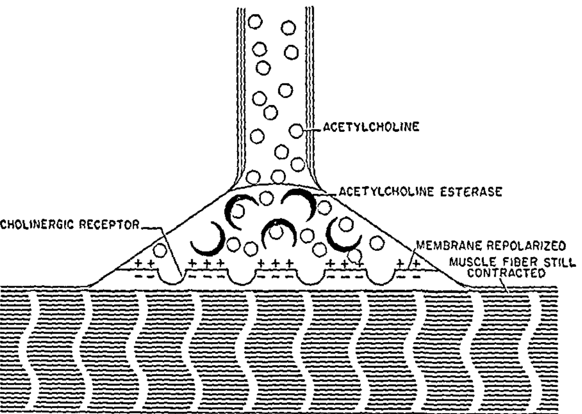


Figure 6. Membrane completely repolarized. Muscle fiber still contracted.

is contracture. Contracture can be defined as a non-propagated sustained contraction that causes considerable shortening of the muscle despite the fact that it is localized to restricted regions of the fibers. It was shown by Kuffler and his coworkers[240,250,227] that the frog muscles which respond to acetylcholine stimulation by contracture are innervated by a system of special small diameter (less than 5 micra) nerve fibers. The contracture-producing action of acetylcholine on the frog muscle can be prevented by atropine and relatively large doses of curare. In contrast to this the twitch, produced by relatively large doses of acetylcholine in the frog sartorius, is not influenced by atropine but is inhibited by small doses of curare.[818]

ACETYLCHOLINE DEPRESSION

Because of the rapid destruction of acetylcholine by acetylcholine esterase at the endplate the depressant effect of acetylcholine on neuromuscular conduction becomes manifest only when its hydrolysis is artificially inhibited. This can be best achieved by the use of cholinesterase inhibitors. The depressant action of acetylcholine was demonstrated by Bacq and Brown[13] by the tetanic stimulation of eserenized muscle. This depressant action is probably due to the spread of the persistent endplate potential to adjacent parts of the muscle fiber.[64] According to Feldberg[138] the possibility cannot be excluded that the persistent depolarization causes changes in the endplate itself and that these changes are responsible for the depression of function.

4

NEUROMUSCULAR BLOCK

Definition. Classification and mode of action of quaternary ammonium type neuromuscular blocking agents. Neuromuscular block by non-depolarizing agents. Neuromuscular block by depolarizing agents. Neuromuscular block by interference with acetylcholine release.

DEFINITION

NEUROMUSCULAR block can be defined as an interference with the transmission of the nerve impulse through the neuromuscular junction to the muscle fibers. As already explained, the depolarization-repolarization sequence mediated by the acetylcholine-acetylcholinesterase system is essential for physiological neuromuscular transmission. Consequently, anything that inhibits the release of acetylcholine at the neuromuscular junction or interferes with either the depolarization or the repolarization of the endplate will cause neuromuscular block. The muscle relaxants in clinical use all belong to the latter group and either inhibit the depolarization or the repolarization phase of neuromuscular transmission. Although agents other than the quaternary ammonium compounds, e.g., tertiary ammonium compounds,[161,27] are also capable of blocking neuromuscular transmission, the clinically used muscle relaxants are all quaternary ammonium compounds.

CLASSIFICATION AND MODE OF ACTION OF QUATERNARY AMMONIUM TYPE NEUROMUSCULAR BLOCKING AGENTS

Several classifications of the quaternary ammonium type neuromuscular blocking agents have been suggested by various investigators. The one by Paton and Zaimis[305,306] distinguishes three types of neuromuscular block: a) competitive block; b) depolarization block, and c) mixed or intermediate block. The classification suggested by Bovet[40] divides the quaternary ammonium compounds into pachycurares and leptocurares. Neither of these two classifications, details of which can be obtained from the references cited, gives a satisfactory explanation of the mechanism of action of neuromuscular blocking agents.

A more recent classification by the author[143] is a modification of the one suggested by Paton and Zaimis and offers a working hypothesis which conforms with most of the presently available experimental findings and which also explains the qualitative and quantitative species variation observed with the quaternary ammonium type neuromuscular blocking agents.

According to this classification[143] the quaternary ammonium type neuromuscular blocking agents can be divided into two groups: a) non-depolarizing, and b) depolarizing agents.

Members of both groups compete with acetylcholine for the cholinergic receptors of the endplate and are capable of preventing the access of acetylcholine to these receptors partly because of their greater stability (they are hydrolyzed either slowly or not at all by cholinesterase) and partly because of their greater affinity to these receptors. After being adsorbed to the receptor proteins[289] the members of the two groups behave differently.

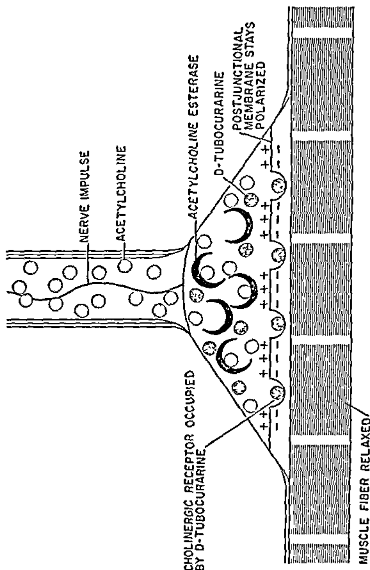


Figure 7. The action of d-tubocurarine and other non-depolarizing muscle relaxants on the neuromuscular junction. Note: a) that the nerve impulse still releases acetylcholine at the endplate but the adsorption of acetylcholine to the cholinergic receptors is prevented by the presence of d-tubocurarine; b) the postjunctional membrane stays polarized and there is no muscle contraction.

The non-depolarizing neuromuscular blocking agents after their adsorption play a wholly passive role, and their activity is limited to the prevention of the access of acetylcholine to the receptors (see Figure 7). The configuration of the receptor proteins remains unchanged, there is no depolarization, no change in the resting potential of the endplate and consequently no muscular contraction. The non-depolarizing agents exhibit a uniform behavior and produce flaccid paralysis in all mammalian, avian, and amphibian species investigated.

The action of the so-called depolarizing neuromuscular blocking agents is not so uniform. In avians, amphibians and some mammals they produce the typical depolarization block described by Paton[64] and his associates. These agents, like acetylcholine, cause depolarization of the endplate (see Figure 8) but in contrast to acetylcholine the depolarization persists, spreads to the parts of the muscle fiber adjacent to the endplate and thereby renders the muscle fiber insensitive to subsequent indirect stimuli. In other mammalian species, however, except for a brief period of depolarization the block produced by these agents shows the characteristics of a non-depolarization block.

The differences in the activity of the two groups of neuromuscular blocking agents can be explained by the following hypothesis: the type of block produced by these compounds depends primarily upon the chemical structure of the agent and secondarily upon the properties of the receptor protein. The structure of the non-depolarizing agents is such that, under physiological circumstances, they will not change the configuration of the receptor proteins and will produce a non-depolarizing block in all species. The block produced by the members of the second group depends on the properties of the

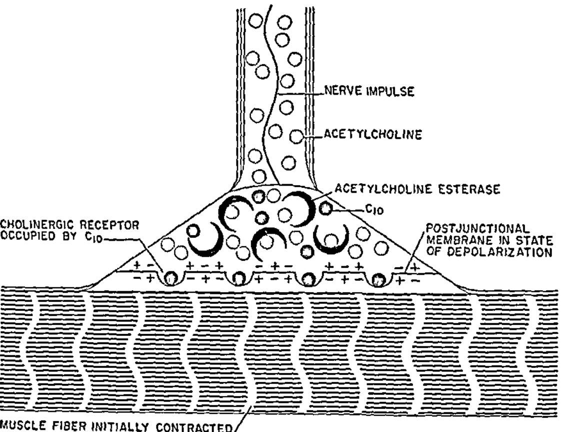


Figure 8. The action of decamethonium or other depolarizing muscle relaxants at the neuromuscular junction. Note: a) that the nerve impulse still releases acetylcholine at the endplate but the adsorption of the acetylcholine to the cholinergic receptors is prevented; b) the postjunctional membrane is depolarized.

TABLE 4

FACTORS DETERMINING THE TYPE OF NEUROMUSCULAR BLOCK PRODUCED BY QUATERNARY AMMONIUM TYPE MUSCLE RELAXANTS

Type of neuromuscular Blocking Agent	*Sensitivity of the receptors towards depolarizing influences*	*Resulting neuromuscular block*
Anti-depolarizing (e.g., d-tubocurarine) uniform activity	Low sensitivity (e.g., monkey)	Anti-depolarization block
	High sensitivity (e.g., cat)	
Depolarizing (e.g., decamethonium) variable activity	Low sensitivity	Anti-depolarization block
	High sensitivity	Depolarization block

receptor protein of the species involved. In some species, where the configuration of the receptor protein can be changed easily, relatively small doses produce depolarization block. In other species where the receptor proteins are more resistant to configuration changes small doses produce no neuromuscular block and large doses cause non-depolarization block.

The sensitivity of the endplate to depolarizing influences can be both increased and decreased under pathological circumstances. Thus in the chronically denervated muscle the endplate becomes more sensitive to acetylcholine[166,101,171] and even non-depolarizing relaxants like d-tubocurarine[236,278,280] or gallamine[60] can cause depolarization. A good example of the decreased sensitivity of the endplate to depolarization is seen in myasthenia gravis[78] where depolarizing relaxants produce a non-depolarization block. The factors which determine the neuromuscular block obtained with the quaternary ammonium type muscle relaxants are summarized in Table 4.

TABLE 5

SPECIES VARIATION OF D-TUBOCURARINE (A TYPICAL NON-DEPOLARIZING MUSCLE RELAXANT) AND DECAMETHONIUM (A TYPICAL DEPOLARIZING MUSCLE RELAXANT)*

The Mg./Kg. Paralyzing Dose

	Cat	*Man*	*Baboon*	*Rabbit*	*Monkey*	*Mouse*	*Rat*	*Frog*
d-Tubocurarine	0.3	0.25	—	0.20	0.09	0.12	0.08	5.5
Decamethonium	0.03	0.05	0.14	0.15	0.25	0.70	2.5	11.0

* From Paton, W. D. M., and Zaimis, E.: *Brit. J. Pharmacol.*, 4:381, 1949.

NEUROMUSCULAR BLOCK BY NON-DEPOLARIZING AGENTS

As already mentioned the non-depolarizing neuromuscular blocking agents inhibit neuromuscular transmission by preventing the access of acetylcholine to the cholinergic receptors of the endplate. Depending on the concentration of these agents at the endplate, more or less of the receptors will be occupied by them, and the magnitude of the endplate potential evoked by the acetylcholine released on indirect stimulation will be proportionately diminished. As the magnitude of the endplate potential diminishes the intensity of muscular contraction decreases, and when the endplate potential falls below a critical level neuromuscular transmission will be completely inhibited.

Under physiological circumstances the neuromuscular block produced by non-depolarizing agents is not preceded by stimulation. These agents cause the same type of block, characterized by flaccid paralysis, in all amphibian, avian, and mammalian species investigated.

The species variation in the mg./kg. dose of the non-depolarizing agents required to produce muscular relaxation in different mammals is relatively smaller than that found with depolarizing agents (see Table 5). There is considerable variation in the sensitivity of various muscles of the same species to the action of non-depolarizing neuromuscular blocking agents.[303] Usually there is an inverse relationship between the sensitivity of the various species, and the different muscles of the same species to non-depolarizing and depolarizing agents.[303] Thus rat and mouse are relatively more sensitive to non-depolarizing agents than to depolarizing drugs, and in cat and man the opposite applies. In the cat, "red muscles" (soleus, diaphragm, intercostals) are more sensitive to d-tubocu-

rarine, a non-depolarizing agent, than to decamethonium, a depolarizing drug, and the sensitivity of the tibialis, "white muscle" to these two types of relaxants is reversed.[304]

Previous tetanization decreases the intensity of the neuromuscular block produced by non-depolarizing agents. In contrast to this tetanization is not well maintained in muscles partially curarized by non-depolarizing drugs; as tetanization progresses, the twitch height gradually diminishes.[304]

The effect of different non-depolarizing muscle relaxants is additive.[324,407] Depolarizing agents however antagonize the neuromuscular block produced by the non-depolarizing muscle relaxants.[110,234,305] Ether and to a lesser extent cyclopropane anesthesia increase the effects of non-depolarizing agents.[188,333,290,342,151] Procaine has a similar effect.[128] Anodal current applied to the endplate also intensifies the block caused by non-depolarizing agents.[305,300]

The neuromuscular block produced by non-depolarizing substances is antagonized by acetylcholine and other depolarizing drugs,[299,305,300] anti-cholinesterases,[296,49,94,246,76] the methyl hydroxyl-phenyl-alkyl ammonium compounds[313,316] (e.g., edrophonium) and other phenolic substances,[282] epinephrine,[297,76] potassium ion,[403] calcium ion[139,75,123] and certain dyes.[241] Anoxia[304] and cathodal current[239] also antagonize non-depolarizing neuromuscular blocking agents.

The effect of the non-depolarizing neuromuscular blocking agents wears off when their concentration at the endplate falls below a critical level that permits the access of acetylcholine to a sufficient number of receptors to produce by depolarization an endplate potential capable of initiating muscular contraction. The decrease of the

concentration of the neuromuscular blocking agents at the endplate will be brought about by redistribution of these agents between the endplate on one hand, and inactive tissue depots of the extracellular compartment and the plasma on the other. This redistribution is brought about by the tendency of the organism to maintain a dynamic equilibrium in the concentration of these agents in various tissues. Consequently, as the concentration of these agents in the plasma decreases, due to excretion, detoxification or both, the direction of the flow will be from the endplate to the plasma. In due course, therefore, the concentration of these agents at the endplate will fall below the critical level, and the neuromuscular block will disappear.

Besides the molar concentration of the non-depolarizing relaxants, the molar concentration of acetylcholine or other depolarizing agents at the endplate as well as the relative affinities of these different molecules to the cholinergic receptors, will determine, according to the rules of mass action whether neuromuscular block will develop or not. Thus, theoretically, there are at least three possibilities for the cessation of neuromuscular block caused by non-depolarizing agents. a) The concentration of the agent at the endplate decreases by redistribution due to excretion, decomposition, or uptake by other tissues below a level at which the acetylcholine present in physiological concentrations at the endplate can generate endplate potential of sufficient intensity to initiate muscular contraction. This is the natural course of events whereby the neuromuscular block terminates without the use of antagonists. b) The concentration of acetylcholine at the endplate can be raised by the use of cholinesterase inhibitors (e.g., neostigmine). The increased number of acetylcholine molecules will displace the molecules of the

neuromuscular blocking agents from the receptors, and the released molecules are carried away by the circulation. This is the primary mode of action of neostigmine, physostigmine and other anticholinesterases. c) The molecules of the non-depolarizing neuromuscular blocking agents may be displaced by molecules of depolarizing substances (e.g., edrophonium) which have a greater affinity to the endplate receptors than the non-depolarizing neuromuscular blocking agents. Here again the released molecules of the relaxant are removed by the circulation from the endplate.

In reality, however, both the "anti-cholinesterase" type (e.g., neostigmine) and the "depolarizing" type (e.g., edrophonium) antagonists of the nondepolarizing muscle relaxants have both anti-cholinesterase and direct depolarizing properties. Thus neostigmine also has a direct depolarizing effect on the endplate,[322] can produce contracture of the frog rectus,[3] and in large concentrations can produce a depolarization block.[49] Edrophonium besides its direct depolarizing effect also has considerable anticholinesterase activity.[347] It is safe to assume that the direct depolarizing effect of the "anti-cholinesterase" type antagonists and the anti-cholinesterase activity of the "depolarizing" type antagonists are also instrumental in bringing about the cessation of the neuromuscular block caused by non-depolarizing relaxants.

NEUROMUSCULAR BLOCK BY DEPOLARIZING AGENTS

The depolarizing neuromuscular blocking agents also compete with acetylcholine for the cholinergic receptors of the endplate (see Figure 8). After adsorption to these receptors their mode of action varies in different species. In amphibians, avians, and certain mammals, in which the

configuration of the receptor proteins changes easily, these agents produce a typical depolarization block.[64,290,300,305] In other mammals, where the configuration of the receptor protein does not change easily,[143] small doses of these agents have little or no effect on neuromuscular transmission and larger doses, after transient depolarization produce a non-depolarization block,[44] the features of which were discussed in preceding paragraphs. In the following the discussion will be confined to the characteristics of the block produced by depolarizing agents in species whose endplate is susceptible to depolarization.

In species where these agents produce prolonged depolarization of the endplate, the depolarization spreads from the endplate to the adjacent parts of the muscle fiber.[64] The depolarized part of the muscle becomes electrically inexcitable[64] and because of the persistent depolarization transmission is inhibited. These agents therefore interfere with the repolarization phase of neuromuscular transmission. The neuromuscular block caused by the depolarizing agents produces spastic paralysis in amphibians[303] and avians[68] and flaccid paralysis preceded by transient stimulation[303,176] in mammals.

There is a very marked (more than eighty fold) species variation in mammals in the mg./kg. paralyzing dose of the depolarizing neuromuscular blocking agents (see Table 5, page 38). However, the variation in the mg./kg. dose, in those species where these agents produce a typical depolarization block (e.g., man, cat), is relatively small. The sensitivity of different muscles of the same species to depolarizing neuromuscular blocking agents also varies.[304] In the cat the sensitivity of the tibialis ("white muscle") to decamethonium is greater than that of the soleus, diaphragm and intercostals ("red muscles"). Factors influencing the activity of neuromuscular blocking

agents usually have an inverse effect on the action of depolarizing and non-depolarizing agents.[304]

Tetanization does not affect the intensity of the neuromuscular block caused by depolarizing agents; tetanus is well maintained in cat muscles in which partial neuromuscular block was produced by decamethonium.[64]

The different depolarizing muscle relaxants have an additive effect[305] and their activity is antagonized by non-depolarizing muscle relaxants.[330,73,264,103] Ether and cyclopropane do not potentiate the neuromuscular effect of depolarizing agents.[151] According to Paton[300] ether and cyclopropane antagonize the neuromuscular block caused by depolarizing agents. Procaine[128] if administered before, antagonizes, if administered after, potentiates the neuromuscular block caused by depolarizing agents. Acetylcholine[300] and anti-cholinesterases[45,259,72,261] increase the neuromuscular blocking activity of depolarizing agents. This is especially true for succinylcholine and other esters with neuromuscular activity that are hydrolyzed by cholinesterase. Edrophonium has either no effect on or potentiates depolarization block.[314,299] Potassium, anoxia or previous tetanization do not antagonize the neuromuscular block produced by depolarizing agents.[305] Anodal current antagonizes, cathodal current potentiates the neuromuscular activity of depolarizing agents.[64]

NEUROMUSCULAR BLOCK THROUGH INTERFERENCE WITH ACETYLCHOLINE RELEASE

Neuromuscular block can also be produced by interference with the acetylcholine release at the nerve ending. Harvey[204] showed that procaine decreases the amount of acetylcholine released at the endplate. It was subsequently reported[55] that calcium deficiency or excess of magnesium,[71a] or phosphate[56] have a similar effect. Guy-

ton and MacDonald[103] found that in nerve muscle preparations poisoned with Botulinus toxin the conduction in the nerve fiber is not affected and the muscle can still be stimulated by the intra-arterial injection of acetylcholine. Subsequently, Burgen *et al.*[61] showed that the quantity of acetylcholine released at the endplate after stimulation of the corresponding nerve is greatly reduced in nerve muscle preparations paralyzed by Botulinus toxins.

5

PHARMACOLOGY OF MUSCLE RELAXANTS

Neuromuscular effect. Central effects. Autonomic effects. Circulatory effects. Miscellaneous effects: Gastro-intestinal tract; respiratory tract; histamine release; cholinesterase inhibition; other effects. Absorption. Toxicity. Excretion. Quantitative analysis.

CLINICAL experience with the use of muscle relaxants has shown that the pharmacological data obtained in animal experiments are not directly transferable to man. Consequently, the pharmacology of muscle relaxants will be discussed in two sections. In the following, a brief summary of the pharmacological data obtained with the muscle relaxants in various laboratory animals will be given. For practical purposes, the pharmacological effects of muscle relaxants in unanesthetized and anesthetized man will be discussed together with the use of the various agents in clinical practice.

NEUROMUSCULAR EFFECT

The myoneural effect of the muscle relaxants has already been discussed in detail in previous chapters. Here the discussion will be limited to the reiteration of a few of the salient points of the neuromuscular effects of these agents.

An outstanding characteristic of the pharmacology of muscle relaxants is their great species variation. This

variation is considerably greater for depolarizing type muscle relaxants than for non-depolarizing agents. This species variation which among mammals is the greatest between cat and rat is three to four fold for d-tubocurarine, a typical non-depolarizing agent, and more than eighty fold for decamethonium, a typical depolarizing agent (see Table 5, page 38).

There is a marked variation in the potency of muscle relaxants not only within different species but also within various muscles of the same species. It has been shown by Paton and Zaimis[304] that, in cat, the soleus and the respiratory muscles ("red muscles") are more sensitive to d-tubocurarine than to decamethonium. In contrast to this, the tibialis ("white muscle") is more sensitive to decamethonium than to d-tubocurarine.

The true non-depolarizing neuromuscular blocking agents, which include d-tubocurarine, dimethyl tubocurarine and gallamine, are antagonized by neostigmine and edrophonium in all animals investigated. The behavior of the depolarizing type neuromuscular blocking agents towards various antagonists is not so uniform. For example, decamethonium is markedly potentiated by neostigmine in the cat and rabbit[219] but it is antagonized by this drug in the monkey,[305] mouse and dog.[220] Similarly, though succinylcholine is markedly potentiated by both neostigmine and edrophonium in the cat, it is only slightly potentiated by the same agents in dogs.[220]

CENTRAL EFFECTS

Opinions regarding the central effects of muscle relaxants are controversial. Salama and Wright[331] found that the direct application 0.1 to 0.2 mg./kg. doses of d-tubocurarine to the central nervous system of cat produced marked excitation. Similarly, McIntyre[277] observed that

curare in subparalytic doses first caused an increase, then a decrease, in the electroencephalographic activity of dogs. McIntyre and his associates[281] reported that ten times the paralyzing doses of d-tubocurarine abolished interneural synaptic transmission in dogs. Recently, Ellis *et al.*[126] found that 0.4 mg./kg. doses of d-tubocurarine injected intravenously in cats depressed spontaneous activity of the respiratory center for considerably longer periods than the duration of the insensitivity of the diaphragm to indirect electrical stimulation. In contrast to these findings, however, curare had no influence on the electroencephalographic tracings of frogs[137,309] and Exerett[133,134] found that five to fifty times the intravenous paralyzing dose of d-tubocurarine had no effect on the electroencephalographic activity of cats, rabbits, or rats. The intracisternal administration of 0.1 mg./kg. d-tubocurarine, however, produced violent convulsions on rabbits.[134] Experimental data on the central effects of muscle relaxants other than d-tubocurarine are very meager. Ellis *et al.*[126] found that decamethonium and succinylcholine had an effect on the respiratory center similar to that of d-tubocurarine. The central effect of succinylcholine seemed to be less pronounced than that of d-tubocurarine and decamethonium.

AUTONOMIC EFFECTS

The autonomic effects of muscle relaxants are due to substrate competition with acetylcholine for the cholinergic receptors of the autonomic ganglia. Of the clinically used muscle relaxants, d-tubocurarine possesses the greatest autonomic activity. In dogs, d-tubocurarine effects preganglionic parasympathetic transmission in lower concentrations than it does preganglionic sympathetic transmission.[195] In dogs curare in myoneural blocking doses inhibits the parasympathetic innervation of the intestines.[189]

The autonomic actions of dimethyl tubocurarine are qualitatively similar to, but less intensive than, those of d-tubocurarine. Thus in the cat the myoneural effect of dimethyl-tubocurarine is eight times greater and its ganglionic effect is six times smaller than those of d-tubocurarine.[314]

With the exception of its inhibitory action on the cardiac vagus, gallamine, in paralyzing doses has little or no effect on ganglionic transmission. Benzoquinonium has little effect on sympathetic transmission. In paralyzing doses it stimulates, and in four to eight times larger doses it inhibits, ganglionic parasympathetic transmission.[219] The autonomic effects of decamethonium are also very weak. One hundred times the neuromuscular blocking dose is necessary for the paralysis of ganglionic transmission in cats.[298] With succinylcholine, 650 to 700 times the neuromuscular blocking dose is required for the complete inhibition of ganglionic transmission.[367]

EFFECTS ON RESPIRATION

Muscle relaxants can influence respiration by paralyzing respiratory muscles, by depressing the activity of the respiratory center, by influencing the chemoreceptors of the carotid body,[254] and by bronchoconstriction due to histamine release.[255]

Experimental evidence indicates that the sensitivity of the diaphragm to muscle relaxants is usually less than that of other muscles.[134,194,359,288,304,40,367] The only exceptions seem to be the increased sensitivity of the dog's diaphragm to gallamine[44] and that of rabbits to d-tubocurarine, gallamine and decamethonium.[229]

As already mentioned, there is considerable disagreement regarding the effects of muscle relaxants on the respiratory center. Harvey[205] reported that in cats curare,

in diaphragm-paralyzing doses, had no effect on the activity of the respiratory center; similar observations were made by Paton and Zaimis[304] in cats. Ellis *et al.*[126] found in cats and dogs, however, that d-tubocurarine, decamethonium and succinylcholine had some effect on the activity of the respiratory center.

Bronchospasm in dogs caused by histamine release was noted after the administration of d-tubocurarine.[255] This complication has not been reported after the use of other muscle relaxants in animal experiments.

CIRCULATORY EFFECTS

Of the clinically used muscle relaxants, d-tubocurarine exhibits the most marked effects on the cardiovascular system. Concentrations of 1 to 4 mg./cc. of d-tubocurarine in the perfusing Ringer solution caused a 2 to 1 atrioventricular block, and concentrations above 5 mg./cc. caused diastolic arrest in frog hearts.[134] Two hundred to 300 times the paralyzing dose of d-tubocurarine caused diastolic arrest in barbitalized dogs;[218] on the other hand, more than 1500 times the paralyzing dose of benzoquinonium was tolerated under similar circumstances.

Cardiac innervation might be affected by several neuromuscular blocking agents. d-Tubocurarine in one and one half times the paralyzing dose blocked the cardiac vagus in dogs.[195] The cardiac sympathetics, however, were found to be ten times as resistant to d-tubocurarine as the myoneural junction. Gallamine has a selective inhibitory action on the cardiac vagus[44,235,324] which seems to be more pronounced in man than in laboratory animals. In dogs, paralyzing doses of gallamine only caused tachycardia when the vagal tone was elevated by previous morphine administration[401] and in cats and rabbits paralyzing doses of gallamine did not accelerate the pulse rate.[111] In con-

trast to gallamine, benzoquinonium has a stimulating effect on the cardiac vagus. Two to 4.0 mg./kg. benzoquinonium caused a 10 to 13 per cent decrease of the heart rate in barbitalized dogs.[251] Thesleff[367] found that succinylcholine in doses below 30 mg./kg. (i.e., 300 times the paralyzing dose) did not affect the heart rate in anesthetized cats, but larger doses caused bradycardia and arrythmia.

Because of its inhibitory effect on ganglionic transmission of the sympathetic vasoconstrictors, d-tubocurarine can produce a marked fall in the blood pressure of various animals. Doses of 0.1 to 0.2 mg./kg. of d-tubocurarine caused a moderate fall and 1.0 mg./kg. doses caused profound hypotension in barbitalized cats and dogs.[134] The blood pressure fall caused by d-tubocurarine can be partially counteracted by epinephrine and ephedrine.[83,134] Because of its effect on sympathetic vasoconstrictors, the histamine liberating properties of d-tubocurarine[88,187,255] can also contribute to the hypotension caused by this agent. In paralyzing doses, benzoquinonium caused moderate elevation of the systolic blood pressure of barbitalized dogs;[251] in much larger doses there was a 20 to 30 per cent decrease of blood pressure. In paralyzing doses, decamethonium has no effect on circulation.[298] Succinylcholine in doses below 1 mg./kg. (10 to 20 times the paralyzing dose) did not affect the blood pressure of anesthetized cats; doses above 2 mg./kg. caused a transient elevation of blood pressure which was proportionately greater with increasing doses.[367] The hypertensive action of succinylcholine could be counteracted by hexamethonium.

d-Tubocurarine and gallamine both exhibited a protective action against epinephrine induced cardiac arrythmias in cats anesthetized with cyclopropane.[324]

MISCELLANEOUS EFFECTS OF MUSCLE RELAXANTS

Gastro-intestinal tract. Decreased peristalsis and intestinal distension were reported after paralyzing doses of d-tubocurarine.[189] Venous congestion and hemorrhage were also observed in the intestinal mucous membranes of dogs after very large doses (i.e., about 50 times the paralyzing dose) of d-tubocurarine.[83] *In vitro,* however, d-tubocurarine increased the motility of rabbit intestine.[134] In moderate doses dimethyl tubocurarine had no effect on the peristalsis in dogs.[359] Gallamine, *in vivo,* had no effect on the intestinal motility of cats.[324] Similarly, benzoquinonium, decamethonium, and succinylcholine have a negligible effect on the tone and motility of the intestinal tract.

Respiratory tract. Muscle relaxants have a variable action on salivation and bronchial secretions in laboratory animals. Secretions are increased more markedly after benzoquinonium than after other neuromuscular blocking agents. Salivation in unpremedicated dogs was also reported after gallamine.[136] No increased salivation or bronchial secretion was observed after succinylcholine in anesthetized dogs, cats or rabbits.[367]

Histamine release. Histamine release is more prone to occur with d-tubocurarine than with any of the other clinically used muscle relaxants. Alam[4] has shown that curare liberated histamine both from normal and denervated skeletal muscle. The histamine released by curare could be responsible for the bronchospasm and severe hypotension observed after its use.[393,83,187,255] Paton[298] only found evidence of histamine release in cats after very large doses of dimethyl tubocurarine. Courvoisier and Ducrot[90] found no evidence of histamine release in dogs following the intravenous administration of one to five times the paralyzing doses of gallamine. Mushin *et al.*[289] working with isolated rat diaphragm found that the

amount of histamine released by gallamine was 1/5 to 1/2 of that released by d-tubocurarine. Histamine release in cats was only observed after the administration of very large doses of decamethonium.[298] No evidence of histamine release was found in cats even after the use of excessive doses (30 mg./kg.) of succinylcholine.[367]

Cholinesterase inhibition. It was reported earlier that d-tubocurarine has negligible inhibitory effect on cholinesterase.[278,199] Recently Vincent and Parant[381a] found that 3.3×10^{-6}M of d-tubocurarine or 1.1×10^{-4}M gallamine caused 50 per cent inhibition of the hydrolysis of acetylcholine by horse plasma cholinesterase. Several hundred times higher concentrations of d-tubocurarine and gallamine were required to inhibit the true cholinesterase obtained from sheep brain. Benzoquinonium also possesses marked anti-cholinesterase activity.[219] Decamethonium has a negligible effect on plasma cholinesterase but it is a fairly potent inhibitor of acetylcholinesterase.[303] Succinylcholine, *in vitro,* inhibits the activity of both the plasma cholinesterase and the acetylcholine esterase.[131,320,–154,206]

Other effects. Urine formation was reported to be diminished by d-tubocurarine in dogs.[260]

Uterine contractions were not affected by paralyzing doses of d-tubocurarine in dogs.[200] The effects of dimethyl tubocurarine on uterine motility of rabbits were moderate and variable.[359] The effect of the other clinically employed muscle relaxants on uterine motility is negligible.

Harroun *et al.*[201] found that curare caused marked hyperglycaemia in unanesthetized dogs.

It has been recently reported that the intravenous administration of succinylcholine causes sustained elevation of the intra-ocular pressure in conscious human volun-

teers,[214a] in anesthetized cats,[257a] and anesthetized man.[257a] The explanation of this phenomenon may well be that the mammalian eye muscles, similarly to certain amphibian muscles, react to succinylcholine with a contracture instead of contraction.

ABSORPTION, ELIMINATION, TOXICITY

Absorption. The absorption of subcutaneously, intramuscularly and intraperitoneally injected d-tubocurarine is relatively good. The paralyzing dose of d-tubocurarine administered by these routes is about two to three times greater than that given intravenously. d-Tubocurarine is fairly well absorbed when administered sublingually,[129] or rectally.[108,371] Dimethyl tubocurarine is also effective when administered subcutaneously. Gallamine is well absorbed after subcutaneous administration, but it is three to four times more effective when injected intravenously.[40] In mice, benzoquinonium is four times less effective when given subcutaneously, and 250 times less active by mouth than when injected intravenously.[218] Decamethonium is also two to three times less effective when given subcutaneously or intramuscularly and 50 to 100 times less potent when taken orally than following intravenous administration.[303,305] The activity of succinylcholine is reduced more than tenfold when administered intraperitoneally.[367] The duration of action of muscle relaxants is markedly increased when administered by other than the intravenous route.

Toxicity. Without artificial respiration the primary cause of death following the administration of muscle relaxants is respiratory arrest. With artificial respiration, however, many times the paralyzing dose is tolerated by laboratory animals. Despite adequate artificial respiration, dogs receiving more than 25 times the paralyzing

dose of d-tubocurarine did not survive.[201] Artificially ventilated rabbits and dogs survived, however, after 500 times the paralyzing dose of gallamine.[42,39] Dogs tolerated more than 1500 times the paralyzing dose of benzoquinonium under similar circumstances.[218] Dogs and rabbits under artificial respiration tolerated 500 to 1000 times the paralyzing dose of succinylcholine.[40]

Excretion. The clinically used muscle relaxants are excreted partly or wholly unchanged in the urine. The proportion of d-tubocurarine excreted unchanged after parenteral administration depends on the species of the test animal. Rats metabolize relatively greater proportions of d-tubocurarine than guinea pigs.[273] The ability of dogs and rabbits to metabolize this agent is somewhere between that of rats and guinea pigs. Dimethyl tubocurarine is metabolized less well than d-tubocurarine and is excreted mostly unchanged in rats[86] and guinea pigs.[273] Thirty to 100 per cent of gallamine could be recovered within two hours in the urine of cats.[288] Over 70 per cent of benzoquinonium administered to barbitalized dogs could be recovered in the urine;[218,219] the fate of the rest of the benzoquinonium is unknown. According to Paton and Zaimis,[305] 80 to 90 per cent of decamethonium administered could be recovered in the urine.

Succinylcholine is hydrolyzed fairly rapidly by various mammalian plasma cholinesterases.[178,45] This hydrolysis occurs in two steps; first, succinylcholine is hydrolyzed at a fairly rapid rate to succinylmonocholine and choline, and then succinylmonocholine is broken down considerably more slowly to succinic acid and choline.[396,372] Because of this hydrolysis, only 5–15 per cent of succinylcholine administered intravenously was found to be excreted unchanged in the urine of cats and mice.[292]

Quantitative analysis. The quantitative analysis of

muscle relaxants can be carried out by biological assay or in some cases by chemical methods. The most frequently used assay method for all muscle relaxants is the rabbit head-drop test of Holaday[215] and its modification.[380] Other methods of biological assay include the frog nerve-muscle preparation of Claude Bernard;[29] the sloping screen method for mice[370,346,412] and rats;[5] the sciatic-gastrocnemius preparation of rats,[263] dogs and cats; the isolated phrenic nerve-diaphragm preparation for rats;[59,283] the isolated frog rectus abdominis preparation;[170] and the young chicken method.[305]

Colorimetric methods for the determination of d-tubocurarine were developed by Mahfouz[267] and Quinn and Woislawski.[311] Marsh[273] described a method for the determination of dimethyl tubocurarine. Benzoquinonium can be determined spectrographically by the method of Martini and Nachod.[274] Decamethonium and other methonium salts can be determined by the colorimetric method of Zaimis.[413] Hestrin's colorimetric method[210] can be adapted to the determination of succinylcholine in plasma.

PART TWO

Clinical Use

6

TECHNIQUE OF ADMINISTRATION OF MUSCLE RELAXANTS

Dosage and timing. Maintenance of adequate respiratory exchange. The choice of muscle relaxants. The use of muscle relaxants with intravenous barbiturates. The use of muscle relaxants with balanced anesthesia: Preoperative medication; anesthetic management. The use of muscle relaxants with inhalation anesthetic agents: The use of muscle relaxants with nitrous oxide or ethylene; the use of muscle relaxants with ether or cyclopropane. The use of different relaxants in the same patients.

DOSAGE AND TIMING

There is a marked variation in the intravenous potency of the clinically used muscle relaxants in man. Because of the considerable difference in the molecular weights of these compounds, the variation is much greater if the dose is expressed on a mg./kg. instead of a moles/kg. basis.[151] Nevertheless for practical purposes, dosages will be discussed in terms of the range of mg. of the initial and the per minute maintenance dose required by average adult patients.

The initial dose of muscle relaxants is influenced by the weight, age, sex, muscularity and various pathological conditions of the patient. The fractional doses, or the

TABLE 6

THE RECOMMENDED RANGE OF THE INITIAL DOSES OF MUSCLE RELAXANTS WITH VARIOUS ANESTHETIC AGENTS

	Range of Initial Doses in Mg. with		
Muscle Relaxant	*Thiopental Sodium*	*Cyclopropane*	*Ethyl Ether*
d-Tubocurarine Chloride	4.5– 18.0	3.0–12.0	1.0– 4.0
Dimethyl Tubocurarine Iodide	1.5– 8.0	1.0– 6.0	0.5– 2.0
Gallamine Triethiodide	40.0–100.0	30.0–80.0	25.0–60 0
Benzoquinonium Chloride	4.5– 18.0	3 5–15.0	2.5–12.0
Decamethonium Bromide	1.0– 4.0	1.0– 4.0	1.0– 4.0
Succinylcholine Chloride	10.0– 50.0	10 0–50.0	10.0–50.0

mg./minute doses necessary for the maintenance of prolonged muscular relaxation, are further affected by the efficiency of the physiological mechanisms responsible for the breakdown or excretion of the various agents.

In general, the initial dose of muscle relaxants, except in the obese, is related to the body weight. It is greater in muscular individuals than in asthenics, in males than in females, and in the young and middle aged than in the aged. Many commonly encountered pathological conditions increase the patient's sensitivity to muscle relaxants and necessitate decreased dosage. Among these conditions are dehydration and electrolyte imbalance,[153] cachexia from malnutrition, chronic infection or neoplastic disease, liver damage[271,131,88] and poisoning with anticholinesterases,[21,271] such as DFP, TEPP etc.

The dose of non-depolarizing muscle relaxants is further influenced by the choice of the general anesthetic agent with which they are used.[151] The potentiating action of

ether on d-tubocurarine is especially pronounced.[188,99] Table 6 summarizes the recommended initial doses of the various muscle relaxants in conjunction with the most frequently employed general anesthetic agents.

It is evident from these considerations that the size of the initial dose of muscle relaxants is influenced by numerous factors and in the final analysis it has to be selected largely on an empirical basis. The personal experience of the anesthetist is of great importance but errors in judgement cannot be avoided even by the most experienced clinicians. When long acting relaxants are used, only after observing the effects of the initial dose and the first fractional dose, also empirically selected, is it possible to determine whether or not the muscle relaxant was administered correctly. The optimal dose of the short acting, hydrolyzable muscle relaxants, when administered in a continuous drip can be determined with greater accuracy.

In general, the long acting muscle relaxants are admin-

TABLE 7

THE RECOMMENDED RANGE OF THE FRACTIONAL DOSES OF MUSCLE RELAXANTS WITH VARIOUS ANESTHETIC AGENTS

	Range of Fractional Doses in Mg. with		
Muscle Relaxant	*Thiopental Sodium*	*Cyclopropane*	*Ethyl Ether*
d-Tubocurarine Chloride	1.5– 6 0	1.0– 4.0	0.5– 1.5
Dimethyl Tubocurarine Iodide	0.5– 3.0	0 5– 2.0	0.2– 0.6
Gallamine Triethiodide	10.0–40.0	10.0–30.0	8.0–20 0
Benzoquinonium Chloride	1.5– 6.0	1.5– 5.0	1.0– 4.0
Succinylcholine Chloride	Administered in continuous drip for prolonged muscular relaxation		

istered intravenously in a single dose, or in an initial dose followed by intermittent fractional doses. The short acting muscle relaxants are used either in a single dose or in continuous intravenous drip. The patient's response to the initial dose of a long acting relaxant is a good guide to the size and time of administration of the first fractional dose. Only after the response to both the initial and the first fractional dose have been observed will the effect of subsequent fractional doses become more or less predictable. The recommended ranges of the fractional doses of muscle relaxants with different general anesthetic agents are shown in Table 7.

In general, diminishing muscular relaxation in the operative field, usually accompanied by an increase in the depth of respiration indicates the necessity for the administration of a fractional dose. To ensure optimal operating conditions, it is a good practice to administer a dose of relaxant just before the start of the closure of the peritoneum. The size of the dose given at this time will be determined by the size of the fractional dose required by the patient, the time interval between fractional doses, and also by the time elapsed since the administration of the last fractional dose. For example, if the fractional dose of gallamine in a patient was 30 mg. administered 20 minutes apart and the last dose was given 10 minutes before peritoneal closure, the dose to be administered at this time should be 15 mg. Usually no more muscle relaxant will be necessary after this dose and the patient's respiration will be normal at the conclusion of surgery.

MAINTENANCE OF ADEQUATE RESPIRATORY EXCHANGE

To obtain intra-abdominal relaxation it is necessary to depress or completely inhibit transmission between the

intercostal nerves and the abdominal muscles. These same nerves, however, also supply the intercostal muscles and the concentration of relaxant which produces abdominal relaxation will also depress, to a variable extent, transmission between the phrenic nerve and the diaphragm. It is therefore unavoidable that relaxation of the skeletal musculature be accompanied by some diminution of the patient's tidal volume. Consequently, whenever muscle relaxants are administered respiration must be assisted to ensure adequate respiratory exchange. Assistance of the patient's respiration is necessary not only to ensure good oxygenation, but also to prevent the accumulation of carbon dioxide and the development of respiratory acidosis. In this respect, it must be remembered that if, for example, a patient's normal tidal volume is 500 cc. and the sum of the physiological dead space and the dead space of the anesthetic equipment is 200 cc. then a decrease of the tidal volume to 300 cc. will decrease effective alveolar ventilation from 300 cc. to 100 cc.

While it is universally accepted that the patient's respiration has to be assisted whenever muscle relaxants are used, opinions diverge widely as to the best method of assistance. Many anesthesiologists feel that controlled respiration should be employed in preference to assisted respiration. Others prefer to retain the activity of the respiratory center and to assist the spontaneous respiratory efforts of the patient. Controlled respiration may be maintained either manually or by the use of various mechanical respirators.

The advocates of controlled respiration claim that: a) occasionally adequate muscular relaxation cannot be obtained without apnea; b) controlled respiration is necessary for the prevention of carbon dioxide accumulation; c) controlled respiration reduces the dose of muscle

relaxant and thiopental sodium necessary for the maintenance of optimal operating conditions;[184,116] d) controlled respiration conserves the patient's energy;[385,184] e) inhibition of the activity of the respiratory center decreases the tone of respiratory muscles,[184] and f) for certain intrathoracic operations, the "quiet chest," that can only be obtained by controlled respiration is a necessity. Furthermore, it is claimed that once the thorax is open spontaneous respiration is inefficient and may be harmful if paradoxical movements are not prevented.[287]

Those preferring assisted respiration maintain that: a) adequate oxygenation and carbon dioxide removal can be achieved with assisted respiration; b) by utilizing the difference between the sensitivity of the human diaphragm and abdominal muscles to muscle relaxants abdominal relaxation can be maintained without apnea;[151] c) intermittent positive pressure control of respiration may interfere with venous return and decrease cardiac output.[269] It is claimed, however, that with intermittent positive-negative pressure respiration this complication can be avoided;[222] d) inhibiting spontaneous respiration deprives the anesthetist of the valuable information that can be gained from respiratory rate, rhythm and tidal volume regarding the depth of anesthesia; e) due to the wide variation in the individual requirements of muscle relaxants and general anesthetic agents, in the absence of the respiratory signs of anesthesia, overdosage with one or both can occur; f) inadequate depth of general anesthesia may be masked by complete neuromuscular block. In contrast to general anesthetic agents the relaxants interrupt the reflex mechanism elicited by painful stimuli on the efferent rather than on the afferant side of the reflex arc. This circumstance will frequently cause changes in cardiac rate and rhythm and blood pressure. Furthermore, an

occasional patient will remember postoperatively the painful stimulation to which he was subjected during surgery; g) occasionally the apnea produced is not readily reversible postoperatively, and either the inability to restore spontaneous respiration[163] or drugs used for this purpose may result in fatalities.[266,81,211]

Space does not allow detailed discussion of the advantages and disadvantages of assisted versus controlled respiration. It can be stated, however, that with careful technique adequate muscular relaxation and respiratory exchange can be maintained with assisted respiration. Unquestionably the greatest danger in using muscle relaxants is prolonged and, on occasion, irreversible apnea, which has been reported most frequently after the use of depolarizing relaxants. The only sure way to avoid postoperative apnea is to abstain from producing apnea during surgery. Consequently, it seems advisable to restrict the use of the apneic technique to those cases when, in the opinion of the surgeon, this is necessary for the production of optimal operating conditions. Whenever the apneic technique is used, care should be exercised to produce apnea with the minimal dose of relaxant that will achieve this purpose to avoid both too deep and too light planes of general anesthesia, and to abstain from hyperventilation resulting in respiratory alkalosis.

THE CHOICE OF MUSCLE RELAXANTS

The selection of the muscle relaxant is influenced by the length of time during which relaxation is necessary, the general anesthetic agent used, and the patient's pathological condition. For procedures like endotracheal intubation or electro-shock therapy where muscular relaxation is only necessary for short periods, the agent of choice is succinylcholine. A single therapeutic dose (0.4 to 0.6

mg./kg.) of this agent will give good muscular relaxation with conditions suitable for endotracheal intubation in about 45 to 60 seconds after its administration.[145] The relaxation lasts about 120 to 240 seconds. Suxethonium, which with somewhat larger doses produces apnea of even shorter duration, may also be used for these purposes.[354] For procedures (e.g., endoscopies, closure of peritoneum, etc.) requiring muscular relaxation for 4 to 12 minutes, a single dose of any one of the long acting muscle relaxants can be used. For the shorter of these procedures, decamethonium, may be employed for the longer ones, gallamine is the drug of preference. For prolonged muscular relaxation either a continuous drip of a dilute (0.1 to 0.2 per cent) solution of succinylcholine or fractional doses of the longer acting muscle relaxants are the most suitable. Because of its minute to minute controllability which allows the almost instantaneous adaptation of the degree of relaxation to the needs of surgery, makes possible the utilization of the difference in sensitivity between the skeletal muscles and the diaphragm, and assures rapid recovery of unimpaired respiratory activity following the discontinuation of the drip, the agent of choice for prolonged muscular relaxation is succinylcholine. This is especially so when combination of thiopental sodium, nitrous oxide-oxygen and analgesics are used for general anesthesia.[360]

When general anesthesia is maintained by an agent like ethyl ether, which in itself has considerable anti-depolarizing activity, the use of the long acting non-depolarizing agents offers a useful combination. Because the synergistic effect of ether is most marked when combined with d-tubocurarine, it can be used with advantage in minimal doses for the production of excellent muscular relaxation with relatively low ether concentrations.[242] This combina-

tion will result in relatively rapid recovery of consciousness because of the low ether concentrations used. Muscular activity will also return promptly because after the elimination of the ether the small doses of d-tubocurarine used will alone, have an insignificant effect on neuromuscular transmission.

As already mentioned (see page 60), certain groups of patients are extremely sensitive to all types of muscle relaxants.[151] Usually the sensitivity is equally present with the long acting agents, the action of which is primarily terminated by urinary excretion, and with succinylcholine which is broken down in the organism by plasma cholinesterase. When long acting non-depolarizing muscle relaxants are used, no matter how carefully, prolonged postoperative respiratory depression, requiring either controlled respiration or the use of antagonists is encountered in about 1 to 2 per cent of the patients.[151] In contrast to this, when succinylcholine is administered carefully in continuous intravenous drip and assisted, instead of controlled, respiration is used prolonged postoperative respiratory depression can be avoided even in patients with extremely low plasma cholinesterase activity.[159]

THE USE OF MUSCLE RELAXANTS WITH INTRAVENOUS BARBITURATES

The analgesic potency of short acting barbiturates is low. Therefore, the use of combinations of these agents with muscle relaxants is recommended only for operative interventions that are not painful. For example, these combinations can be safely used for pelvic examinations, the correction of dislocations and fractures, manipulation of joints and electroshock therapy. Since neither the intravenous barbiturates nor the muscle relaxants are

capable of depressing the reflex irritability of the pharynx, larynx and trachea, these structures should be topically anesthetized before induction of anesthesia. The details of the anesthetic management with such combinations will be discussed in an ensuing chapter.

The use of thiopenthal sodium solutions containing fixed proportions of d-tubocurarine,[14,15,16] decamethonium[293] and gallamine[132] have been recommended by various anesthesiologists. The d-tubocurarine-thiopenthal sodium mixture employed by Baird[15] is prepared by dissolving 0.5 gm. of thiopenthal sodium in 15 cc. of distilled water and adding to it 5 cc. of d-tubocurarine chloride solution (3 mg./cc.). Each cc. of this mixture contains 0.75 mg. of d-tubocurarine and 25 mg. of thiopenthal sodium. The decamethonium-thiopenthal sodium mixture suggested by Organe[293] contains 4 mg. of decamethonium and 1.0 gm. thiopenthal sodium dissolved in 20 or 40 cc. Evans and Gray[132] use an 0.2 per cent thiopenthal sodium solution containing 0.5 mg. of gallamine per cc. after induction of anesthesia with 0.5 gm. of thiopenthal sodium and 80 mg. of gallamine. Although it cannot be denied that using a single solution containing both the intravenous anesthetic agent and the muscle relaxant simplifies the task of the anesthetist, on the basis of both pharmacological considerations and clinical experience the use of such fixed mixtures does not seem to be justified. It is a common experience that there is a great variation in both the thiopenthal sodium and muscle relaxant requirements of patients. The sensitivity towards muscle relaxants and intravenous anesthetic agents do not always parallel one another. For example, an asthenic individual who consumes alcohol regularly, or is used to sedatives and analgesics will require relatively large doses of thiopenthal sodium and small doses of muscle relaxant.

TABLE 8

RELATIONSHIP BETWEEN THIOPENTAL SODIUM AND DECAMETHONIUM REQUIREMENTS

	Thiopental Sodium-Decamethonium Ratio Range	Average
Before intubation	100–300	224
For total length of anesthesia	81–300	160

On the other hand, muscular young adults might need relatively large doses of muscle relaxants and small doses of intravenous anesthetic agents. Furthermore, in operations of long duration, after the administration of the initial dose, the muscle relaxant requirements per unit of time are about the same. In contrast to this, the mg. per minute thiopenthal sodium requirements are inversely proportional to the length of anesthesia.[345] Calculation of the ratios of the thiopenthal sodium and decamethonium doses used before intubation and during anesthesia revealed that there is a wide variation in these ratios in different individuals, and that the average ratio before intubation is considerably greater than the average ratio during the whole anesthetic procedure[144] (see Table 8).

THE USE OF MUSCLE RELAXANTS WITH "BALANCED ANESTHESIA"

In the majority of cases muscle relaxants are used in combination with short acting intravenous barbiturates, nitrous oxide-oxygen and intravenously administered narcotic analgesics. In such combinations each agent is used for its primary effect in minimal effective doses. Thus, the intravenous barbiturates will be mainly responsible for the production of amnesia and sleep; nitrous oxide and the analgesics will supply analgesia; and the muscle relaxants will contribute the relaxation necessary for

many surgical procedures. These methods combine pleasant and rapid induction of anesthesia with excellent operating conditions without undue depression of vital functions; and rapid, smooth return to consciousness. Different combinations of barbiturates, analgesics and muscle relaxants have been recommended by various workers. The description of all the various techniques (which usually differ from one another only in minor details) is beyond the scope of this monograph. In the following paragraphs the techniques proved to give the best results in the author's experience will be discussed in detail.

Preoperative medication. At bedtime on the night before operation 50 to 200 mgs. of phenobarbital or pentobarbital is administered. One and one half to 2 hours before the start of anesthesia 50 to 200 mg. of a short acting barbiturate (e.g., pentobarbital) is given either by mouth or intramuscularly; this is followed by an intramuscular injection of 50 to 100 mg. of meperidine hydrochloride and 0.2 to 0.6 mg. of scopolamine hydrobromide or 0.4 to 1.0 mg. of atropine sulphate.

Anesthetic management. On arrival in the operating room, an intravenous infusion is started through a No. 19 to 17 needle with 5 per cent dextrose in water or 5 per cent dextrose in physiological saline. The patient's mouth and pharynx are topically anesthetized with a 1 per cent tetracaine hydrochloride or 5 per cent cyclaine solution. Thiopenthal sodium is then administered (in 2.5 per cent solution, through a No. 22 needle inserted into the rubber sleeve of the intravenous infusion) until the patient will tolerate the insertion of an oro-pharyngeal airway. This is followed by the administration of oxygen by a face mask and if the patient's respiratory exchange is adequate, indicating the absence of excessive central depression, the appropriate dose of the selected muscle relaxant is admin-

istered again through the rubber sleeve of the intravenous tubing. During the time required for the development of muscular relaxation suitable for endotracheal intubation oxygen is administered with manual assistance of the respiration. When the depression of the respiratory tidal volume indicates the development of muscular relaxation, the patient is briefly hyperventilated with oxygen, the mask and oropharyngeal airway are removed, the cords are exposed by direct laryngoscopy and sprayed under vision with the local anesthetic agent. If the cords are relaxed and spraying does not provoke coughing, the endotracheal tube is inserted. Otherwise, an additional small dose of the muscle relaxant, thiopenthal sodium, or both, are administered, the airway is reinserted and assisted respiration with oxygen is continued for an additional 1 to 2 minutes until adequate relaxation for intubation is obtained. Following intubation, the endotracheal tube is connected, directly or through a face mask applied over it to the anesthesia machine. After a few breaths of oxygen a mixture of approximately 25 to 35 per cent oxygen and 65 to 75 per cent nitrous oxide is administered. Such a mixture can readily be obtained by flushing the apparatus three times with a 3 to 4 liter nitrous oxide and 1 liter oxygen and then using a flow of 500 cc. nitrous oxide and 500 cc. oxygen per minute.[150] Where the patient's oxygen requirements are expected to be high, or the use of higher oxygen concentrations is indicated, the oxygen flowmeter is set at 600 or 700 cc./min. When, for some reason (e.g., inadequate closure) higher flow rates are indicated, the setting of the oxygen flowmeter can be readily calculated from the following formula: Oxygen flowmeter setting =

$$300 + \left(\frac{\text{Desired total flow} - 300}{100}\right) \times \text{desired oxygen}$$

concentration. The setting of the nitrous oxide flowmeter = total flow — oxygen flowmeter setting.

Additional doses of muscle relaxant are administered whenever increasing respiratory depth or the diminishing relaxation of the operative field indicate the need. The administration of about one third of the initial dose of the relaxant will maintain, depending on the agent used and other variables, satisfactory relaxation for 10 to 30 minutes. To obtain optimal conditions for peritoneal closure, the fractional dose or the appropriate portion of it, is injected (see page 62). With this method of administration relaxation will be maximal, when it is most needed, at the time of peritoneal closure, it will decline gradually from then on and will usually have worn off completely by the time surgery is concluded.

When changes in the rate or rhythm of respiration, voluntary breath holding or other signs indicate the lightening of general anesthesia, small doses of a short acting potent analgesic, alphaprodine (Nisentil) hydrochloride are injected intravenously.[345] The average initial dose varies between 5 to 15 mg. Repeated doses of 5 to 10 mg. are administered until the necessary depth of anesthesia is reached. If this stage cannot be obtained without depressing the respiratory rate below 12/minute, the anesthesia is deepened by administering additional small doses of thiopenthal sodium. Alphaprodine administration is not resumed until the respiratory rate reaches at least 16/minute. It should be emphasized that an increase of the respiratory rate alone is not an indication, but only a guide, to the further administration of alphaprodine or thiopenthal sodium. Depending on the experience of the anesthetist with the method, 50 to 95 per cent of the patients will respond to vocal or tactile stimuli within 5 minutes of the end of the nitrous oxide administration.

Earlier, instead of alphaprodine, meperidine (Demerol) was used for the supplementation of nitrous oxide-oxygen, thiopenthal sodium anesthesia.[291a,51a,286] In our experience the following technique was found to be suitable for the use of meperidine. Depending on the patient, 15 to 30 cc. of 2.5 per cent thiopenthal sodium is administered before the first dose of 12.5 to 25 mg. meperidine is given. From then on every 5 to 10 ml. of 2.5 per cent thiopenthal sodium is followed by another 12.5 to 25 mg. dose of meperidine. Attempts to maintain adequate depth of general anesthesia after an initial dose of thiopenthal sodium with meperidine alone frequently results in respiratory depression and prolonged postoperative recovery.

An alternative method is to use larger doses of alphaprodine and considerably smaller doses of thiopenthal sodium. The unwanted respiratory depression produced by the large doses of alphaprodine are antagonized by levallorphan tartrate (Lorfan). Previous investigations showed that levallorphan when administered 4 to 6 minutes before alphaprodine in a 1 to 50 ratio counteracts the respiratory depressant effects of the latter.[157,361] It was subsequently found that the use of levallorphan tartrate in this proportion causes little change in the hypnotic and analgesic effects of alphaprodine.[160]

After the usual preparation, 0.01 to 0.02 mg./kg. of levallorphan (1.2 to 1.6 mg. for the average adult) is administered intravenously, followed in 4 to 6 minutes by 0.5 to 1.0 mg./kg. of alphaprodine injected intravenously in 30 seconds. Subsequently, a mixture of 3 to 4.0 liters/minute of nitrous oxide and 1 liter/minute of oxygen is administered to the patient. After 3 to 4 minutes, if the depth of general anesthesia permits it, an oro-pharyngeal airway is inserted. If at this time the depth of general anesthesia is inadequate but the respiratory rate and

depth are satisfactory, one or more 5.0 to 15.0 mg. doses of alphaprodine are injected until satisfactory depth of anesthesia is obtained or the respiratory rate approaches 12 per minute. In the latter case, 2 to 6 cc. of 2.5 per cent thiopenthal sodium is injected intravenously in 2 cc. increments. Following the insertion of the oro-pharyngeal airway, the bag of the anesthesia machine is again washed out 3 times with the 4.0 to 1.0 liter/minute nitrous oxide-oxygen mixture and then the flowmeters are set to deliver 500 cc./minute of nitrous oxide and 500 cc./minute of oxygen.

Further doses of alphaprodine are administered as required. Occasionally, if the alphaprodine requirements are great, or in prolonged operations it will be necessary to administer one or more additional 0.3 to 0.5 mg. doses of levallorphan. Additional small doses of thiopenthal sodium are given when adequate depth of anesthesia cannot be maintained without undue depression of the respiratory rate. This in our experience occurred rarely. If the patient is to be intubated, the use of 2 to 8 cc. of 2.5 per cent thiopenthal sodium before intubation is advisable.

The advantages of the combined use of alphaprodine and levallorphan are: (1) The respiratory tidal volume is less depressed than after the administration of thiopenthal sodium alone or in combination with analgesics. (2) The patient's sensorium is much clearer immediately after termination of anesthesia than after other combinations. (3) There is considerable residual analgesia without any respiratory depression in the immediate postoperative period. A somewhat different technique is employed when succinylcholine is used to provide prolonged relaxation (see page 110).

Due to the light planes of general anesthesia produced

by these techniques elevation of the systolic blood pressure is occasionally encountered. The administration of small doses (5 to 10 mg.) of hexamethonium bromide repeated if necessary will usually return the systolic blood pressure to preoperative levels.

Whenever a muscle relaxant is used, the patient's tidal volume will invariably be diminished, necessitating continuous assistance of the respiration. Such assistance should consist of the application of enough slow, gradual pressure on the breathing bag during the patient's spontaneous inhalation to obtain a tidal volume of about 500 to 800 cc. If the patient's respiratory rate is greater than 24 per minute, the assisting of every other respiration is sufficient to prevent carbon dioxide accumulation. Too vigorous assistance of respiration may result in hypocapnia and respiratory alkalosis.

THE USE OF MUSCLE RELAXANTS WITH INHALATION ANESTHETIC AGENTS

Two different approaches may be selected for the management of anesthesia when muscle relaxants are the management of anesthesia when muscle relaxants are used in conjunction with inhalation agents. The first method involves the induction of anesthesia with a short acting intravenous barbiturate, the administration of the relaxing dose of a neuromuscular blocking agent, endotracheal intubation, and the administration of the inhalation agent through the endotracheal tube. With the second technique, anesthesia is induced by the administration of the inhalation agent and when the desired light plane of anesthesia is reached, muscular relaxation is obtained by the administration of a suitable relaxant. With both methods the goal is the production of muscular relaxation, without the deep planes of general anesthesia

which would be required if inhalation anesthetic agents alone were to be used for this purpose.

The use of muscle relaxants with nitrous oxide or ethylene. In the presence of adequate oxygen concentrations in the inhaled gas mixtures, neither nitrous oxide nor the somewhat more potent ethylene will invariably give sufficient depth of anesthesia to prevent the perception of painful stimuli. Despite this, the use of nitrous oxide-oxygen with muscle relaxants alone without any other hypnotics and analgesics has been recommended,[168] for the production of general anesthesia for various surgical procedures. The advocates of this method produce complete neuromuscular block by the use of large doses of relaxants and take control of the patient's respiration. With this technique the protective reflex mechanism activated by painful stimuli is interrupted between the efferent pathway (motor neuron) and effector organ (muscle) while the afferent pathways are little affected and central perception may not be satisfactorily depressed. Occasionally the patient may feel and later remember the painful stimulation originating in the operative area but, because of the total muscular paralysis, will be unable to bring his harrowing experience to the attention of the anesthetist. Beside the danger of severe psychic trauma disturbing the patient's postoperative course, marked circulatory changes and bronchospasm can occur during surgery under such circumstances.

Consequently, the use of nitrous oxide or ethylene alone is not generally recommended for the production of general anesthesia in conjunction with muscle relaxants. In the occasional debilitated, poor risk patient with markedly decreased pain sensitivity, it may be possible to produce suitable operating conditions by the combination of

nitrous oxide-oxygen or ethylene-oxygen alone with a muscle relaxant. In these cases, however, the anesthetist must be sure before the administration of the muscle relaxant that satisfactory depth of general anesthesia has been reached and the administration of the relaxant should not be pushed to the point of total muscular paralysis and apnea.

Far more satisfactory operating conditions can be obtained with less danger to the patient if the general anesthesia produced by these gases is supplemented by small intravenous doses of short acting analgesics, barbiturates or both.

The use of muscle relaxants with ether or cyclopropane. Muscle relaxants can be safely and effectively used to supplement ether or cyclopropane anesthesia. Here again, techniques utilizing assisted rather than controlled respiration are recommended. With controlled respiration the most valuable sign of general anethesia, the respiratory activity, will be absent and under the cover of apnea the patient may receive dangerously high concentrations of these potent inhalation anesthetic agents. Under such circumstances severe circulatory depression, or in extreme cases, cardiac arrest may develop.

The potentiating effect of ether, and to a lesser extent that of cyclopropane, on the activity of the non-depolarizing muscle relaxants must be kept in mind. This is especially important when anesthesia is induced by a short acting barbiturate and a full dose of d-tubocurarine is used for the facilitation of endotracheal intubation. Subsequent administration of ether intensifies and prolongs the effect of d-tubocurarine and often leads to prolonged apnea. It is usually safer and more satisfactory to induce the desired level of anesthesia with ether or cyclopropane

and then administer the correct dose of the muscle relaxant selected. As already mentioned, both from the pharmacological and clinical point of view the muscle relaxant of choice for use with ether anesthesia is d-tubocurarine (see page 66). Dimethyl tubocurarine or gallamine can also be used for this purpose because their neuromuscular activity is additive to that of ether. The depolarizing muscle relaxants are less suitable for the production of prolonged muscular relaxation with ether anesthesia.

Since the anti-depolarizing activity of cyclopropane at the motor endplate is not as marked as that of ether, both non-depolarizing and depolarizing muscle relaxants can be used for the production of prolonged muscular relaxation with this agent.

When the operative procedure does not require prolonged relaxation but rather rapid induction and early endotracheal intubation before the start of the administration of ether or cyclopropane, the muscle relaxant of choice is succinylcholine combined with a short acting barbiturate. Owing to the brief duration of its action, when given in the correct dosage, respiratory activity will become adequate shortly after intubation and provided that adequate topical anesthesia of the airway has been produced, the administration of the inhalation agent can proceed smoothly.

THE USE OF DIFFERENT RELAXANTS ON THE SAME PATIENT

The effect of the various non-depolarizing relaxants is additive and the same is also true for depolarizing relaxants. Consequently, no serious objection can be raised against the use of more than one depolarizing or non-depolarizing relaxant in the same patient in the course of

one anesthesia. For example, succinylcholine may be used for endotracheal intubation; relaxation could then be maintained by decamethonium, and another dose of succinylcholine could be administered to facilitate peritoneal closure. The interchange of the various non-depolarizing muscle relaxants has little to offer since there is not much difference in the duration of action of these agents. Changing from d-tubocurarine to gallamine might be indicated if the administration of the former is accompanied by signs of histamine release (e.g., bronchospasm).

Changing from a non-depolarizing relaxant to a depolarizing agent or vice versa, however, is in general not a sound practice. Depolarizing and non-depolarizing relaxants should only be used after one another if the pharmacological effect of the one first used has been completely dissipated. While this will only take a few minutes after moderate doses of succinylcholine, the effects of even moderate doses of non-depolarizing relaxants (e.g., the effects of 10 mg. of d-tubocurarine) are still demonstrable after 45 minutes, so that at this time one half of the initial dose will produce an identical effect with that of the original dose.[375]

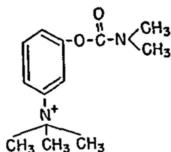
Before a depolarizing relaxant (e.g., decamethonium or succinylcholine) is able to produce neuromuscular block in the presence of clinically ineffective concentrations of a non-depolarizing agent at the neuromuscular junction, it has to overcome the residual inhibition of the physiological depolarization caused by the latter.[303] Therefore, larger doses of depolarizing relaxants are necessary to produce muscular relaxation in an individual who has just recovered from the effects of a non-depolarizing drug. Once the large dose of a depolarizing drug does produce a block under these circumstances, its duration may be greatly prolonged[234] and can result in prolonged postoperative apnea.

7

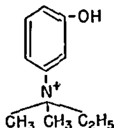
THE USE OF THE ANTAGONISTS OF MUSCLE RELAXANTS

Mode of action. Indications. Dosage. Time relationships. Side effects and complications. Recommended clinical use.

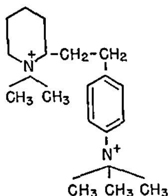
As discussed in Chapter 4, both the non-depolarizing and depolarizing muscle relaxants are antagonized by a variety of agents. In clinical practice, however, antagonists are usually employed only against the non-depolarizing muscle relaxants. Neostigmine (Prostigmin) methyl sulphate and edrophonium (Tensilon) are the two drugs used most frequently for this purpose. In contrast to their effect on the neuromuscular block caused by the non-depolarizing muscle relaxants, in man both neostigmine and edrophonium usually intensify and prolong the neuromuscular block produced by depolarizing muscle relaxants. Another agent, B.W. 49-204 (1-meth[illegible] methylamino-[illegible] has been sho[illegible] muscular bloc[illegible]onium both in animal experiments[107] and in man.[379] Ellis *et al.*[127] reported that benzhydryl piperazines are capable of antagonizing the neuromuscular effect of succinylcholine. Of the compounds tested n-methyl-N-ethyl-N-benzhydryl piperazinum iodide (B.W. 51-212) was the most active.[81] The



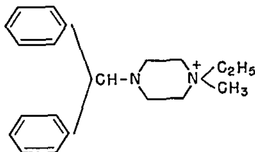
NEOSTIGMINE
$C_{12}H_{19}N_2O_2$



EDROPHONIUM
$C_{10}H_{16}NO$



B W 49 - 204
$C_{18}H_{32}N_2$



B W 51 - 212
$C_{20}H_{27}N_2$

Figure 9. The structural formulae of the antagonists of muscle relaxants

structural formulas of the antagonists of muscle relaxants are shown in Figure 9.

MODE OF ACTION

It is generally accepted that the antagonistic effect of neostigmine on the neuromuscular block produced by non-depolarizing muscle relaxants depends primarily on its anti-cholinesterase activity.[31] Because of the inhibition of

cholinesterase at the neuromuscular junction the concentration of acetylcholine will become high enough to displace the muscle relaxants from the endplate and thereby re-establish neuromuscular conduction. Opinions differ as to the mode of action of edrophonium. Some investigators believe that the action of edrophonium depends primarily on its ability to stimulate the endplate directly.[323,389] Hobbiger[213] and Smith *et al.*[347], however, are of the opinion that the relatively weak but definite anti-cholinesterase activity of edrophonium is responsible for its anticurare activity. Randall[313] entertained the possibility that the free phenolic group[282] present in edrophonium might be in part responsible for the anti-curare activity.

INDICATIONS

Neostigmine and edrophonium have been recommended to counteract the respiratory depression caused by the non-depolarizing muscle relaxants at the end of anesthesia,[1,62,11,112,231] to terminate muscular relaxation after unexpectedly short operations,[112] endoscopies[330] and electroshock therapy.[135]

Both neostigmine and edrophonium are capable of antagonizing the neuromuscular block caused by d-tubocurarine, dimethyl tubocurarine, gallamine and laudexium. They are also effective against other non-depolarizing muscle relaxants.

DOSAGE

There is considerable variation in the recommended therapeutic doses of neostigmine. Macfarlane *et al.*[264,265] found that 0.75 mg. neostigmine injected intravenously partially antagonized the effect of d-tubocurarine doses that produced 95 per cent decrease in the grip strength of

unanesthetized man. The effect on vital capacity was more marked than on grip strength.[264] Doughty and Wylie[112] and Hunter[231] suggest the use of 1.25 to 2.5 mg. doses of neostigmine accompanied by 0.65 to 1.3 mg. doses of atropine sulfate. Hunter[231,232] favors the larger doses of atropine.

The recommended dose of edrophonium varies from 5 to 20 mg.[11,112] Hunter[231] advises the use of a 0.65 mg. dose of atropine sulfate with edrophonium too. In general, the greater the degree of curarization the larger should be the initial dose of neostigmine or edrophonium. Some investigators[112,231] believe that edrophonium is less effective in deeply curarized patients than in those where the effect of the muscle relaxant has already started to wear off. If the general anesthetic agent used with the muscle relaxant is ether, larger doses of edrophonium[11] are necessary than if it is cyclopropane or nitrous oxide-oxygen with thiopenthal sodium; the same is also true for neostigmine.

TIME RELATIONSHIPS

The time interval between the intravenous injection and the development of effect is shorter for edrophonium[11,265] (30 to 60 seconds) than for neostigmine[112,264,306] (120 to 240 seconds). The duration of action of edrophonium is also shorter[265,112,231] than that of neostigmine. Recurarization following the temporary improvement of neuromuscular activity can occur with edrophonium[112,231] and occasionally also with neostigmine.

SIDE EFFECTS AND COMPLICATIONS

The side effects and possible complications of both neostigmine and edrophonium are primarily due to their

muscarinic properties, caused by the action of an excess of acetylcholine on the postganglionic component of the parasympathetic system. These are more marked with neostigmine than with edrophonium and can be mitigated by the prophylactic use of atropine.

The greatest danger reported after the use of neostigmine is marked slowing of the heart rate which in extreme cases may cause fatalities through cardiac arrest.[266,81,211] Hunter[232] found that the bradycardia observed after the administration of neostigmine, is usually preceded by moderate short lasting tachycardia. The bradycardia is less marked with edrophonium especially if general anesthesia is maintained by ether.[11]

Other undesirable side effects, also more pronounced after neostigmine than edrophonium, include excessive salivation and bronchial secretion, bronchiolar spasm, and intestinal hypermotility. This latter complication has been reported to be especially dangerous following surgery of the gastro-intestinal tract.[112]

Besides the muscarinic effects of neostigmine and edrophonium, another danger of their use lies in the possibility of recurarization in a seemingly recovered patient who is left unobserved.[151] This complication, because of its shorter duration of action, is more likely to arise with edrophonium than with neostigmine. In large doses[310a] neostigmine itself may produce myoneural black.

RECOMMENDED CLINICAL USE

With the correct selection and method of administration of muscle relaxants the use of antagonists should seldom be necessary. If the respiratory exchange or muscle tone at the termination of surgery, despite all precautions, is inadequate it is by far safest to oxygenate the patient by assisted respiration until satisfactory spontaneous respira-

TABLE 9

THE RECOMMENDED DOSE OF THE ANTAGONISTS OF NON-DEPOLARIZING MUSCLE RELAXANTS

Agent	*Initial Dose Mg. Antagonist*	*Atropine*	*Onset of Action Min.*	*Repeat* Dose Mg.*	*Time Interval Between Doses*
Neostigmine	0.5–1.5	0.4–0.6	2–4	0.5–1.0	5–8
Edrophonium	1.0–2.0	0.3–0.6	0.5–1	5.0	2–4

* If initial dose does not produce desired effect.

tion is re-established. Should it become necessary for some reason to administer an antagonist, the following safeguards are recommended:

The initial dose of neostigmine, depending on the size and physical condition of the patient, should be between 0.5 to 1.5 mg. in adults and proportionately less in children. Atropine sulphate, 0.4 to 0.6 mg. should precede the injection of neostigmine. If, after 5 minutes this dose did not produce satisfactory effects, one half of the initial dose can again be administered. The initial dose of edrophonium is 5 to 20 mg. (less in children). An 0.3 to 0.6 mg. dose of atropine sulphate, although not absolutely essential, is recommended to ensure against the possibility of muscarinic side effects. If the desired effect is not obtained within 2 minutes, additional 5 mg. doses can be given. Patients to whom antagonists of muscle relaxants have been administered should be kept under close supervision for 30 to 60 minutes after return of adequate respiration to ensure against the possibility of re-curarization. The suggested methods of administration of neostigmine and edrophonium are summarized in Table 9.

The clinical use of the syncurine antagonist B.W. 49-204 has been described by Vandam *et al.*[379]

8

/ COMPLICATIONS OF THE USE OF MUSCLE RELAXANTS: THEIR CAUSES, PREVENTION AND TREATMENT

Respiratory complications: Apnea; bronchospasm; excessive salivation and bronchial secretion. Circulatory complications: Hypotension; hypertension; change in rate and rhythm; cardiac arrest. Decreased peristalsis and intestinal distention. Muscular twitching.

When employed judiciously, cognizant of their pharmacological effects, other than those exerted at the neuromuscular junction, the muscle relaxants will increase rather than decrease the safety of the patient. The improper selection of the muscle relaxant or the administration of excessive doses of the agent of choice, however, may lead to serious complications and will occasionally endanger the patient's life. In general, the complications caused by muscle relaxants are due to: a) excessive and prolonged action at the neuromuscular junction; b) their effect on ganglionic autonomic transmission, or c) their ability to liberate histamine from the tissues. These complications may occur both during and after anesthesia and can affect the respiratory and circulatory systems, the gastro-intestinal tract or the voluntary muscles.

RESPIRATORY COMPLICATIONS

Apnea. Although the apneic technic of administration of muscle relaxants is practiced by many anesthesiologists, in the opinion of others, apnea, especially when produced inadvertently by the overdose of a muscle relaxant should be considered a complication. Whenever it occurs, measures for its correction should be instituted without delay because the only safe and certain prevention of prolonged postoperative apnea is the prevention of prolonged apnea during anesthesia.

Apnea in the course of anesthesia can be produced by different mechanisms, and it is by no means always caused by an overdose of the muscle relaxant used. Besides the accidental overdose of the muscle relaxant, usually caused by overestimation of the patient's need, apnea can also be produced by the depression of the respiratory center by the agents used for premedication and general anesthesia, by the development of excessive carbon dioxide tension in the patient[319] and by a combination of the above factors. Too vigorous controlled respiration might cause apnea by decreasing the carbon dioxide tension below the level necessary for the stimulation of the respiratory center. The hypocapnia caused by hyperventilation will decrease urea excretion[349] and the accumulation of blood urea will tend to increase the depth of barbiturate anesthesia[118] and cause secondary depression of the respiratory center. It has been suggested that prolonged stimulation of the pulmonary stretch receptors during positive pressure controlled respiration may send, through the vagi, "out of phase" impulses to the respiratory center. These artificial impulses might interfere with the pattern of physiological excitation of the respiratory center and inhibit its "auto-rhythmicity."[113] It is conceivable that under such circumstances the respira-

tory center will not resume its normal activity for prolonged periods after discontinuation of positive pressure controlled respiration. Finally, the presence of an endotracheal tube, especially if inserted too near to the carina without the use of a topical anesthetic agent, may produce reflex breath-holding in vagotonic individuals in too light planes of general anesthesia.

Debilitated and dehydrated patients, especially in the presence of potassium deficiency, show an increased sensitivity to non-depolarizing neuromuscular blocking agents.[152] It is probable that this increased sensitivity is due to lack of potassium since it is known that potassium has an antagonistic effect on the neuromuscular block caused by curare.[403] For reasons to be discussed later, such patients are also hypersensitive to succinylcholine. To avoid prolonged respiratory depression in these patients long acting muscle relaxants should only be administered in repeated small doses or, better still, relaxation should be maintained by the administration of a slow drip of a dilute succinylcholine solution. The patient's respiratory exchange must be continuously observed by manual palpation of the breathing bag of the anesthesia machine, and as soon as the decreased tidal volume indicates the development of neuromuscular block the drip should be slowed to the rate that will just maintain adequate muscular relaxation. If at any time apnea develops, the drip should be stopped until spontaneous respirations return. In the meanwhile the administration of about 500 to 800 cc. of gas mixture 12 to 14 times per minute by intermittent manual compression of the breathing bag will take care of the oxygen requirements and prevent carbon dioxide accumulation without producing hypocapnia. Consequently, with the return of neuromuscular transmission in the respiratory muscles the respiratory center of the

patient will be capable of taking over control of spontaneous respiration.

The prolonged postoperative apnea or respiratory depression encountered in a small percentage of the cases following the use of long-acting non-depolarizing muscle relaxants can be treated by the careful administration of neostigmine-atropine or edrophonium-atropine mixtures (see page 85). In refractory cases the intravenous administration of an 0.3 per cent potassium chloride solution may be helpful. Since the decreased urinary excretion that frequently accompanies anesthesia and surgery[63] might prolong the effect of those relaxants (gallamine, benzoquinonium, decamethonium) that are excreted primarily unchanged in the urine, use of an osmotic diuretic (e.g., hypertonic glucose) is also indicated in such cases.

The combined effects of premedication and the short acting barbiturates can produce apnea during induction. When this occurs, the administration of the muscle relaxant should be postponed until the patient resumes spontaneous respiration. Otherwise, it may be difficult to determine later in the course of anesthesia whether the apnea is due to central depression or to neuromuscular block. Later in anesthesia apnea caused by depression of the respiratory center may also develop because of carbon dioxide accumulation caused by inefficient respiratory exchange. This can be avoided by the supplementation of patient's respiratory tidal volume to about 500 to 800 cc. by manual compression of the breathing bag during inspiration and keeping the respiratory rate above 12 per minute. Carbon dioxide accumulation may develop in the presence of seemingly adequate minute volumes if these are obtained by rapid but shallow breathing. Not infrequently the analgesics used to supplement nitrous oxide-oxygen, thiopenthal sodium anesthesia depress the

respiratory center and cause apnea. This complication can be avoided by using short acting analgesics in repeated small doses[345] or by combining a respiratory antagonist with the analgesic[160] (see page 72).

Too vigorous controlled respiration may tend to perpetuate apnea by several different mechanisms. Hyperventilation can lead to hypocapnia and thereby remove the physiological stimulus of spontaneous respiratory activity. *This can be corrected by decreasing both the* rate and depth of controlled respiration and allowing the accumulation of carbon dioxide to the level necessary for the stimulation of the respiratory center. Hypocapnia caused by hyperventilation will tend to increase sodium and especially potassium excretion and decrease urea excretion.[349] The potassium loss will tend to potentiate the effect of non-depolarizing muscle relaxants and the decreased urea excretion will increase the effect of thiopenthal sodium.[118] Both these changes increase the possibility of apnea; the potassium loss by increasing neuromuscular paralysis, the decreased urea clearance by deepening central depression. Prolonged and too energetic controlled respiration can also cause apnea by exhausting the Herring-Breuer reflex. When this occurs, distension of the alveoli will not initiate expiration and inspiratory apnea results.[197]

In extreme cases of hypoventilation, in addition to carbon dioxide accumulation, hypoxia may also develop. Pronounced hypoxia will further depress the sensitivity of the respiratory center.[410]

In too light planes of general anesthesia vagal stimulation caused by the presence of an endotracheal tube might cause reflex breath holding. This is more prone to occur if inadequate doses of atropine or scopolamine are used in premedication, topical anesthetization of the

larynx and trachea is not done, or the tube is inserted close to the carina. Vagotonic constitution of the patient and the presence of acute or chronic respiratory disease predispose to this complication. It can usually be remedied by deepening the plane of general anesthesia or by the administration of additional doses of a parasympatholytic drug. Occasionally, however, the apnea induced by this mechanism can only be corrected by removal of the endotracheal tube.

The prolonged apnea occasionally encountered with succinylcholine is caused by a combination of factors which are somewhat different from those already considered. Because of its great practical importance, succinylcholine apnea will be considered in greater detail in the chapter on succinylcholine (see page 115).

Bronchospasm. In connection with the use of muscle relaxants, bronchospasm is most frequently encountered with the use of d-tubocurarine. It is caused by histamine release.[255] It is more prone to occur in patients suffering from bronchial asthma or other allergic conditions. In such patients bronchospasm can also occur with other relaxants especially when general anesthesia is maintained with thiopenthal sodium or cyclopropane and if the plane of general anesthesia is too light. There is no reason to believe that in such cases the relaxant is the cause of the bronchospasm. The administration of an antihistaminic instead of a short acting barbiturate in premedication may be effective in preventing the bronchospasm in patients with allergic conditions. Immediate relief can be obtained from bronchospasm by the intravenous injection of 0.1 to 0.2 mg. of epinephrine diluted to 5 cc. The relief can usually be maintained by the slow intravenous injection of 250 to 300 mg. of aminophylline or the slow intravenous infusion of 1 mg. of epinephrine dissolved in 500 cc. of

5 per cent dextrose in water. Should bronchospasm develop under cyclopropane anesthesia, epinephrine must not be used. Aminophylline may be used under such circumstances. In asthmatic patients it may be necessary to change over to oxygen-ether anesthesia to overcome bronchial spasm.

Excessive salivation and bronchial secretion. Excessive salivation and bronchial secretion are encountered most frequently with benzoquinonium and less frequently with d-tubocurarine. Their incidence with the other muscle relaxants is low. A generous dose of atropine or scopolamine used in premedication will usually prevent this bothersome, but seldom serious, complication.

CIRCULATORY COMPLICATIONS

The circulatory complications reported to have been caused by muscle relaxants include hypotension,[187] hypertension,[156] change in pulse rate[12,156] and cardiac arrest.[153]

Hypotension. Hypotension has been reported most frequently with d-tubocurarine, dimethyl tubocurarine and laudexium. It is caused by ganglionic blocking action, histamine release or the combination of these two factors.[134,88,187,255] The incidence of hypotension with clinical doses of these relaxants is low and its intensity is seldom great. In sensitive patients, however, the blood pressure fall may be severe and prolonged enough to necessitate counter-measures. Nor-epinephrine will counteract both the ganglionic blocking component and the histaminic component of the pressure fall. The ganglionic sympathic inhibition and histamine release caused by other clinically used muscle relaxants are negligible and do not lead to hypotension. When hypotension is encountered with these agents, its cause should be looked for elsewhere. Decreased cardiac output due to hypoxia, too deep planes

of general anesthesia, controlled respiration with intermittent positive pressure[269] or non-replaced blood loss may be responsible for the hypotension, especially in patients with cardiovascular pathology.

Hypertension. Hypertension resulting from the use of muscle relaxants occurs most frequently with gallamine and succinylcholine. It is usually encountered in patients with labile hypertension, especially if carried in too light planes of general anesthesia. The hypertension is commonly accompanied by acceleration of the pulse rate. After gallamine, the tachycardia and rise in pressure are probably due to the selective inhibition of the cardiac vagus.[324,11,156] Although in cats succinylcholine in 20 times the paralyzing dose had no effect on ganglionic autonomic transmission,[367] larger doses caused a moderate rise in blood pressure; therefore, the possibility cannot be excluded that in certain sensitive individuals succinylcholine in clinical doses may stimulate ganglionic sympathetic transmission. The elevation of blood pressure with succinylcholine can be effectively counteracted by the intravenous administration of 5 to 10 mg. of hexamethonium.

Acceleration of the heart rate. Acceleration of the heart rate is almost invariably encountered with gallamine. In contrast to this, the use of benzoquinonium occasionally causes bradycardia.[325]

Cardiac arrest. The effect of muscle relaxants on the myocardium is negligible. Depending on the relaxant used, 200 to 1500 times the paralyzing dose can be administered intravenously before the development of cardiac arrest.[218] It is therefore, safe to assume that the cessation of cardiac activity, when muscle relaxants are being used, is not due to the direct action of these agents on the myocardium, but it is rather caused by either inadequate oxygenation of the myocardium or myocardial

depression caused by excessive concentrations of the general anesthetic agent used. Myocardial hypoxia can be caused by hypoxemia, severe anemia, decreased cardiac output with inadequate filling of the coronaries or, most frequently, by a combination of two or more of the above factors.

Excessive blood concentration of the anesthetic agent is most likely to be encountered with the too rapid injection of thiopenthal sodium during induction of anesthesia. Too high concentrations of cyclopropane and ether are most likely to occur if they are administered with controlled respiration when in the absence of respiratory signs the depth of anesthesia cannot always be estimated accurately.[147]

Endotracheal intubation and extubation are the periods when cardiac arrest occurs most frequently. Excessive doses of barbiturates used for induction and the apnea produced by large doses of muscle relaxants, considered by many anesthesiologists essential for atraumatic intubation, are mainly responsible for cardiac arrest developing during induction. Reflex breath holding, due to inadequate topical anesthetization of the larynx, might also be a contributing factor. The longer the time consumed by attempts to pass the endotracheal tube, the greater is the likelihood that trouble will develop in the presence of one or more of the above complicating factors. Observing the following precautions will tend to prevent the development of cardiac arrest during intubation: (1) Except with ether use topical anesthesia on the pharynx and larynx when endotracheal intubation is contemplated in the course of anesthesia. (2) Allow 3 to 4 minutes for the induction of anesthesia with intravenous barbiturates. (3) Check the circulation after induction before adminis-

tering the muscle relaxant. (4) Try to use a dose of relaxant that will provide good relaxation of the jaw and larynx without complete apnea. (5) Hyperventilate the patient with oxygen prior to intubation. (6) Spray the cords and the trachea with a local anesthetic agent under direct vision before intubation. (7) Should intubation prove difficult do not persist for more than 30 seconds in attempts to pass the endotracheal tube. Oxygenate the patient and allow a few minutes' rest before attempting intubation once more. (8) Oxygenate the patient again immediately after intubation.

During extubation prolonged, uninterrupted suction and obstruction of the airway after removal of the endotracheal tube are the most likely causes of anoxia and cardiac arrest. If ventilation has been inadequate and carbon dioxide has accumulated during anesthesia, with the return of normal alveolar ventilation rapid decrease of the carbon dioxide tension in the tissues may cause a precipitous fall in blood pressure. This will contribute to the inadequate oxygenation of the myocardium and to the development of cardiac arrest. Sudden changes in the cardiac rate and rhythm foreshadows more serious trouble and should never be treated lightly.

DECREASED PERISTALSIS AND INTESTINAL DISTENSION

This complication is occasionally seen with d-tubocurarine[189] but is rarely encountered with the other muscle relaxants. The instillation of 20 to 30 cc., one per cent 2-chloroprocaine or procaine dissolved in 5 per cent dextrose in water into the peritoneal cavity will usually cause the dilated intestines to constrict.

TWITCHING

Muscular twitching is often seen immediately after the administration of depolarizing muscle relaxants. It occurs more frequently with succinylcholine than with decamethonium. It is due to short tetanic contractions of the muscle fibers[64] caused by the rapid depolarization of the end plate. When large doses of succinylcholine are administered rapidly, not only twitching but vigorous clonic contractions of the limb muscles can also occur. The convulsions may be severe enough to cause definite post-anesthetic muscle pain, especially in ambulatory patients.[77] With slow injection of smaller doses post-anesthetic muscle pain is not encountered in hospitalized patients.

9

SPECIAL CONSIDERATION OF THE MUSCLE RELAXANTS MOST FREQUENTLY USED IN ANESTHESIOLOGY

d-Tubocurarine chloride. Dimethyl tubocurarine (Metubine, Mecostrin). Gallamine triethiodide (Flaxedil). Benzoquinonium chloride (Mytolon). Decamethonium bromide (Syncurine). Succinylcholine chloride (Anectine). Miscellaneous muscle relaxants: Laudexium methyl sulfate (Laudolissin), Suxethonium bromide (Brevedil "E").

D-TUBOCURARINE CHLORIDE

ALTHOUGH pure d-tubocurarine was already isolated from tube curare by King in 1935,[244] the first standardized curare extracts were prepared in the laboratories of A. R. McIntyre in 1938–39[277] from crude curare samples brought to the United States by R. C. Gill.[172] (See structural formula in Figure 1, on page 15 and physical and chemical properties in Table 2 on page 18.) At McIntyre's suggestion this extract was used by A. E. Bennett and his collaborators[25] for prevention of trauma in shock therapy.

With the help of the rabbit head-drop test of Holaday,[215,380] a highly purified and standardized curare preparation, Intocostrin, was prepared in the laboratories of E. R. Squibb and Sons. This preparation was first used to produce muscular relaxation during anesthesia by Griffith

and Johnson in 1942[186] on the instigation of Dr. L. H. Wright. Shortly thereafter, crystalline d-tubocurarine chloride, previously isolated by King from tube curare,[244] was prepared by Wintersteiner and Dutcher[408] from Chondodendron tomentosum and became available for clinical use.

d-Tubocurarine is the classical example of a non-depolarizing muscle relaxant. It prevents the adsorption of acetylcholine to the cholinergic receptors of the endplate thereby inhibiting the changes in the endplate potential which are essential for the initiation of muscular contraction (see page 39).

When given to conscious human volunteers, in doses up to 14 mg., d-tubocurarine only affected neuromuscular transmission[375] and had no effect on blood pressure, pulse rate, electrocardiogram, electroencephalogram, pain threshold or mental reactions. No central stimulant, depressant or analgesic action was observed in a volunteer even after 2.5 times the paralyzing dose of d-tubocurarine.[351] Unna and his associates[374] found that a 9 to 10 mg. dose of d-tubocurarine, that depressed the grip strength by 95 per cent, reduced vital capacity about 30 per cent. Grip strength recovered to 75 per cent of the original value in about 27 minutes. Vital capacity had returned almost to the control value by this time.

In the anesthetized patient, in addition to the neuromuscular effect, d-tubocurarine can also produce undesirable side effects, such as hypotension, by its action on autonomic transmission[195] and may also cause histamine release from tissues.[4]

The neuromuscular effect of d-tubocurarine is markedly potentiated by ether[188] and to a lesser extent by cyclopropane. The effect of d-tubocurarine is additive with those of other non-depolarizing muscle relaxants.[407,324]

Physostigmine,[296] neostigmine[40,94] and edrophonium[316,313] as well as potassium ion[403] are capable of antagonizing the neuromuscular action of d-tubocurarine.

d-Tubocurarine is usually injected intravenously after induction of anesthesia but before endotracheal intubation, except in infants in whom it can be administered intramuscularly in 0.15 mg./kg. doses before the start of ether administration.[350] Details of the technique of its administration are described on page 59). The dosage and time relationships of the administration of d-tubocurarine are summarized in Table 10.

Because of the synergism between the two agents d-tubocurarine is the muscle relaxant of choice with ether anesthesia. Owing to the small doses of d-tubocurarine necessary for the production of relaxation with ether neuromuscular block will wear off rapidly and spontaneous respiration will become normal as fast as ether is eliminated from the body.

TABLE 10

THE DOSE AND TIME RELATIONSHIPS OF D-TUBOCURARINE ADMINISTRATION

General Anesthetic Agent	*Initial Dose* *In Mg.*	*Development of Maximal Effect* *In Min.*	*Fractional Dose* *In Mg.*	*Time Interval Between Fractional Doses* *In Min.*	*Recovery After Last Dose* *In Min.*
Thiopental Sodium					
Nitrous Oxide	6–18	3–5	2–6	15–30	20–35
Ethylene					
Cyclopropane	4–15	3–5	2–5	15–30	15–25
Ether	2–5	2–4	1–2	15–30	5–15

d-Tubocurarine has been recommended[67] to counteract the reflex bradycardia and hypotension caused by the carotid sinus, pulmonary plexus, celiac plexus, pelvo-laryngeal and pelvo-cardiac reflexes. This beneficial effect of curare results from the depression of ganglioic parasympathetic transmission.[195] The dose of d-tubocurarine necessary for this effect depends on the anesthetic agent used and also the patient. With ether anesthesia, small (1 to 3 mg.) doses may give the desired effect. With other anesthetic agents the necessary vagal inhibition can only be obtained with apneic doses.

Because of its histamine releasing properties the use of d-tubocurarine is contraindicated in patients with history of bronchial asthma or other allergic disorders. Its use should also be avoided in cases where even a transient drop of blood pressure would be dangerous.

The prevention and treatment of the complications that may occasionally accompany the use of d-tubocurarine have been discussed on page 86. Because of its importance to the patient's safety, a brief resume of the treatment of postanesthetic respiratory depression might be in place. With few exceptions, the safest method of dealing with postanesthetic respiratory depression is the continuation of the manual assistance of the patient's breathing with 100 per cent oxygen until spontaneous respiration becomes adequate. Care must be taken that the assisted or controlled respiration should not result in either excessive carbon dioxide accumulation or in hypocapnia since both may contribute to the prolongation of the respiratory depression. If neostigmine or edrophonium is to be used to hasten the return of spontaneous respiration the pharmacological properties of these potent drugs must be considered. Both drugs, especially neostigmine, stimulate the parasympathetic nervous system and may

cause bradycardia, hypotension, bronchospasm, increased intestinal motility and cardiac arrest, if not preceded by a prophylactic dose of atropine. The single intravenous dose of neostigmine should not exceed 1.5 mg. and that of edrophonium 20 mg. These amounts should be injected slowly over 30 to 60 seconds preceded by an adequate dose of atropine sulfate (see page 80). The patients should be kept under close observation for at least 30 minutes after the return of spontaneous respiration because, due to the relatively short duration of action of neostigmine and especially that of edrophonium, recurarization might occur.

DIMETHYL TUBOCURARINE (*Metubine, Mecostrin*)

Dimethyl tubocurarine is a non-depolarizing muscle relaxant. It was first prepared from d-tubocurarine by King.[244] It is available either as the chloride or iodide salt. (See structural formula in Figure 1 on page 15, and physical and chemical properties in Table 2, on page 18.)

In unanesthetized man the active cation is about two and a half times as potent as d-tubocurarine.[376] It has a relative sparing effect on respiration; a 4.0 mg. dose of dimethyl tubocurarine iodide depressed the grip strength of the unanesthetized human volunteer 90 per cent but decreased tidal volume by only 16 per cent.[376] The duration of its action in unanesthetized man is somewhat shorter than that of d-tubocurarine. Half the standard dose repeated 45 minutes after the initial dose, however, usually had the same effect as the initial dose.[306] Except for its neuromuscular activity, no pharmacological effects were observed with a 4.0 mg. dose of dimethyl tubocurarine iodide in unanesthetized man.[375] Compared with its neuromuscular effect, the histamine liberating and

TABLE 11

THE DOSE AND TIME RELATIONSHIPS OF DIMETHYL TUBOCURARINE ADMINISTRATION

General Anesthetic Agent	*Dose Initial* *In Mg.*	*Development of Maximal Effect* *In Min.*	*Fractional Dose* *In Mg.*	*Time Interval Between Fractional Doses* *In Min.*	*Recovery After Last Dose* *In Min.*
Thiopental Sodium					
Nitrous Oxide	2.5–8.0	3–5	1.0–3.0	15–35	20–35
Ethylene					
Cyclopropane	2.0–6.0	3–5	1.0–2.0	15–35	15–25
Ether	1.0–3.0	3–5	0.5–1.0	15–35	5–15

autonomic blocking action of dimethyl tubocurarine is relatively less than that of d-tubocurarine.[84,405] It has been clinically evaluated by Stoelting and his collaborators[357,358] and others.[106,209]

The neuromuscular effect of dimethyl tubocurarine is potentiated by ether and cyclopropane and antagonized by neostigmine and edrophonium.

The technique of administration of dimethyl tubocurarine is the same as that of other long acting muscle relaxants (see page 59). The dosage and time relationships of its administration are summarized in Table 11.

The indications and contraindications of the use of dimethyl tubocurarine are similar to those of d-tubocurarine (see page 99).

GALLAMINE TRIETHIODIDE *(Flaxedil)*

In their search for synthetic muscle relaxants with more selective neuromuscular activity, Bovet and his collabo-

rators[42] developed gallamine triethiodide (Flaxedil) which became the first widely used synthetic neuromuscular blocking agent. (See structural formula in Figure 1, on page 16 and physical and chemical properties in Table 2, on page 18.) Its use in anesthesiology was first reported by Huguenard and Boue[223] and later by Mushin and his associates.[288] The pharmacology of gallamine was described by Bovet *et al.*[44] and by Riker and Wescoe.[324]

Gallamine belongs to the group of non-depolarizing blocking agents. Its neuromuscular effect is counteracted by neostigmine[288] and edrophonium.[11,270] It is potentiated by ether.[151,352]

Gallamine was studied in conscious volunteers by Mushin *et al.*[288] and by Unna *et al.*[374,375] The average dose that produces 95 per cent reduction in the grip strength

TABLE 12

CIRCULATORY CHANGES WITH THE USE OF GALLAMINE

	Pulse Rate		*Systolic Blood Pressure mm. Hg.*		*Diastolic Blood Pressure mm. Hg.*	
	Range	*Average*	*Range*	*Average*	*Range*	*Average*
Initial	51–130	88.6	72–240	120	40–120	72
10 minutes after start of anesthesia	72–155	97.6	60–230	118	.40–140	74
Lowest value observed during anesthesia	53–118	88.0	65–160	108	20–100	66
Highest value observed during anesthesia	75–172	111.0	95–240	139	50–150	91
At the termination of anesthesia	70–172	99 0	80–210	128	40–120	80

is about 50 mg., five times greater than the corresponding dose of d-tubocurarine. This dose causes about 20 per

cent decrease of vital capacity.[374] The average duration of its action in unanesthetized volunteers is shorter, than that of d-tubocurarine.[374] Systolic and diastolic blood pressure and pulse rate increase moderately after paralyzing doses of gallamine.[374] The administration of one half the original dose of gallamine 45 minutes after the first dose produces identical effects with the initial dose.

Besides its neuromuscular action, the only significant effect of gallamine is on blood pressure and pulse rate,[253,270,156] both of which are consistently elevated with its use. These changes encountered in 330 consecutive patients in whom muscular relaxation was maintained with gallamine are summarized in Table 12.[156]

The method of administration of gallamine is the same as that of other long acting relaxants (see page 59). The dose and time relationships with various anesthetic agents are summarized in Table 13.

TABLE 13

THE DOSE AND TIME RELATIONSHIPS OF GALLAMINE ADMINISTRATION

General Anesthetic Agent	*Initial Dose In Mg.*	*Development of Maximal Effect In Min.*	*Fractional Dose In Mg.*	*Time Interval Between Fractional Doses In Min.*	*Recovery After Last Dose In Min.*
Thiopental Sodium					
Nitrous Oxide	40–100	3–5	10–30	15–30	20–35
Ethylene					
Cyclopropane	30–80	3–5	10–25	15–30	20–30
Ether	25–60	3–5	5–20	15–30	15–25

Of the long acting muscle relaxants, gallamine is the muscle relaxant of choice with cyclopropane anesthesia. Not only does it tend to counteract the bradycardia fre-

quently seen with cyclopropane but it also has some protective action against the cardiac arrythmias occasionally seen with this agent.[324] Although no ill effects have been observed after the use of gallamine in known cardiac patients[156] because of the persistent elevation of blood pressure and pulse rate observed with its use, it is not recommended in the presence of cardiovascular disorders and hyperthyroidism.

The prevention and treatment of the respiratory depression occasionally encountered with gallamine is the same as that with other non-depolarizing muscle relaxants and is described on page 84.

BENZOQUINONIUM CHLORIDE *(Mytolon)*

Benzoquinonium was synthetized by Cavallito and his collaborators.[74] (See structural formula in Figure 1 and physical and chemical properties in Table 2.) Its pharmacological properties in animals were described by Hoppe.[218] It was used for the production of muscular relaxation in anesthetized patients by Arrowood,[10] Foldes and his coworkers,[141,152] Hunter[232] and others.

In contrast to d-tubocurarine, dimethyl tubocurarine and gallamine which produce a typical non-depolarization block that can be antagonized by edrophonium and cholinesterase inhibitors, the activity of benzoquinonium is less uniform. The neuromuscular block produced by benzoquinonium in man is little if at all antagonized by neostigmine.[232,180]

The dose and time relationships of benzoquinonium administration are summarized in Table 14.

Besides its neuromuscular blocking action, benzoquinonium stimulates the vagus, causing a marked increase in salivary and bronchial secretions and a tendency to bradycardia. These side effects of benzoquinonium can be

prevented by using larger doses of atropine or scopolamine in premedication or by administering additional doses of atropine during anesthesia.[10,141]

TABLE 14

THE DOSE AND TIME RELATIONSHIPS OF BENZOQUINONIUM ADMINISTRATION

General Anesthetic Agent	*Initial Dose In Mg.*	*Development of Maximal Effect In Min.*	*Fractional Dose In Mg.*	*Time Interval Between Fractional Doses In Min.*	*Recovery After Last Dose In Min.*
Thiopental Sodium					
Nitrous Oxide	4.5–18.0	6–8	1.5–6.0	15–20	15–25
Ethylene					
Cyclopropane	4.0–15 0	6–8	1.0–6.0	15–20	15–20
Ether	3.0–12.0	6–8	1.0–4 0	15–20	10–15

Its use is contraindicated in acute or chronic respiratory disease or in patients with disturbances of cardiac conductivity.

DECAMETHONIUM BROMIDE (*Syncurine*)

Decamethonium was synthetized independently by Barlow and Ing[19] and Paton and Zaimis.[302] (See structural formula in Figure 1, on page 17 and physical and chemical properties in Table 2 on page 18.) Its pharmacology was studied extensively in various species by Paton and his collaborators.[303,64,305] It was first used in clinical anesthesia by Organe *et al.*[294]

The activity of decamethonium in conscious volunteers was investigated by Unna and his associates.[370,306] They found that an average of 2.24 mg. of decamethonium depressed the grip strength of volunteers by 95 per cent of

the control value, though the variation in the size of the dose producing this decrease was greater than with other relaxants. The same dose depressed vital capacity 61 per cent so that in unanesthetized man the respiratory depressant effect of decamethonium was about 2, 3, and 4 times greater than that of d-tubocurarine, dimethyl tubocurarine, and gallamine respectively. The time necessary for 75 per cent recovery of grip strength with decamethonium was about 20 minutes. With the exception of succinylcholine, it has the shortest duration of action of all the commonly used muscle relaxants. While on repeated administration d-tubocurarine, dimethyl tubocurarine, and gallamine showed evidence of cumulation, repeated administration of decamethonium after 30 minutes consistently caused a decreased response in conscious volunteers. This tachyphylaxis could not be demonstrated in animals or in anesthetized man.[144]

Decamethonium is a suitable relaxant for the production

TABLE 15

THE DOSE AND TIME RELATIONSHIPS OF DECAMETHONIUM ADMINISTRATION

Initial Dose In Mg.	*Development of Maximal Effect* In Min.	*Fractional Dose* In Mg.	*Time Interval Between Fractional Doses* In Min.	*Recovery After Last Dose* In Min.
1.0–4.0	4–6	0.5–1.0	10–20	15–25

of muscular relaxation for moderately short procedures (e.g., endoscopies). The dose and time relationships of decamethonium are independent of the general anesthetic agent used and are summarized in Table 15.

The effect of decamethonium tends to wear off abruptly. When administered over prolonged periods and in large

doses postanesthetic return of normal respiratory exchange may be delayed.[183,229] This complication may also occur with the use of moderate doses.[198,144]

SUCCINYLCHOLINE CHLORIDE *(Anectine)*

Succinylcholine was first synthetized by Hunt and Taveau in 1906.[228] (See structural formula in Figure 1, on page 17 and physical and chemical properties in Table 2, on page 18.) Its neuromuscular activity was discovered by Bovet and his collaborators[43] and by Phillips.[308] The first clinical trials with succinylcholine were reported by Brücke *et al.*,[58] Thesleff,[364] and Mayrhofer and Hassfurther.[276]

Succinylcholine is a depolarizing muscle relaxant. Its neuromuscular blocking action is frequently preceded by muscular twitching or contracture of muscle groups. The intensity of the contractures depends on the size of the dose and the rate of its injection. In contrast to the other clinically used muscle relaxants, succinylcholine is almost completely hydrolyzed in the organism by plasma cholinesterase, first fairly rapidly to succinylmonocholine and choline[396,372,148] and then much more slowly to succinic acid and choline. The average rate of the enzymatic hydrolysis of succinylcholine is about 3.0 micromoles per 1.0 cc. of plasma in 30 minutes.[158] Succinylmonocholine is hydrolyzed about 6 to 7 times slower than succinylcholine.[148] Succinylmonocholine has an inhibitory effect on the enzymatic hydrolysis of succinylcholine.[373] Following its intravenous administration in 1.0 mg./kg. doses or in continuous drip, capable of producing muscular relaxation for abdominal surgery, less than 3 per cent of the total dose of succinylcholine is excreted unchanged in the urine of anesthetized pa-

tients.[146] The true cholinesterase of human red cells does not hydrolyze succinylcholine.[206]

Succinylmonocholine, the primary breakdown product of succinylcholine, also has neuromuscular blocking activity.[148,155] In anesthetized man the intravenous injection of succinylmonocholine-iodide in 5 to 7 mg./kg. doses produced good muscular relaxation in 3 to 5 minutes. The relaxation lasted 8 to 12 minutes and could be maintained by the intravenous injection of 3 to 5 mg./kg. doses 8 to 12 minutes apart.[155] Following its administration in relaxant doses, 12–14 per cent of succinylmonocholine was excreted unchanged in the urine.[146]

In relaxant doses, provided that adequate carbon dioxide removal is ensured succinylcholine only affects neuromuscular conduction. No evidence of histamine release or ganglionic activity can be demonstrated under such circumstances after its use.

The effect of succinylcholine in unanesthetized man was described by Mayrhofer[275] who used it in 0.125 to 0.5 mg./kg. doses. When injected rapidly, paralysis was preceded by muscular twitching if the dose was 0.25 mg./kg. or greater. When injected slowly (over a 2 minute period), no fibrillation developed even after 0.5 mg./kg. doses. In the 0.125 to 0.5 mg./kg. dose range succinylcholine only affected neuromuscular conduction and had no effect on sensorium, blood pressure, heart rate, or electrocardiogram. The rapid injection of 0.375 mg./kg. of succinylcholine was painful.

Succinylcholine is the muscle relaxant of choice both for very short and very long procedures. For the production of muscular relaxation not to exceed 3 minutes the dose of succinylcholine is 0.3 to 0.6 mg./kg. When administered to an anesthetized patient in 15 to 30 seconds the 0.3 mg./kg. dose will produce adequate muscular

relaxation, suitable for endotracheal intubation, within about 45 seconds from the end of injection and lasting about 60 seconds. With this dose apnea in normal individuals will either be absent or of less than 60 seconds duration. Muscular twitching is observed only infrequently with this dose and method of administration. The intravenous injection of 0.6 mg./kg. of succinylcholine in 30 seconds is almost invariably followed by slight muscular twitching and apnea averaging about 180 seconds.[158] The intravenous administration of a 1.0 mg./kg. dose caused apnea lasting an average of 500 seconds in anesthetized patients.[146] In patients with low plasma cholinesterase activity the duration of apnea may be prolonged 2 to 3 fold after an 0.6 mg./kg. dose.[159] Consequently, the single dose of succinylcholine should be reduced to from one third to one half of the normal dose in patients in whom decreased plasma cholinesterase activity is expected. Decreased plasma cholinesterase is frequently encountered in liver disease; severe anemia; hypoproteinemia; cachexia due to malnutrition; malignancy or chronic infection; and in poisoning with cholinesterase inhibitors (e.g., certain weed killers, war gases).[271,131,21]

The intramuscular use of succinylcholine in 2 mg./kg. doses with hyaluronidase or 4 mg./kg. doses without it has also been recommended[276a] primarily for infants and children (see page 138).

When succinylcholine is to be employed for the production of prolonged muscular relaxation, it should be administered in continuous intravenous drip of an 0.1 to 0.2 per cent solution.[104,275,153] Following induction of anesthesia (see page 70), oxygen or nitrous oxide-oxygen is administered through a face mask and the succinylcholine drip is started at a fairly rapid rate (180 to 240 drops of an 0.1 to 0.2 per cent solution, about 9 to 18 mg./minute)

in patients with normal plasma cholinesterase activity, and at a considerably slower rate of the 0.1 per cent solution in patients suspected to have low plasma cholinesterase level. Muscular relaxation with depression of the respiratory tidal volume develops in 2 to 3 minutes. The onset of relaxation can be followed by palpation of the breathing bag. When the decrease of the respiratory depth indicates adequate relaxation, and apnea is not essential for atraumatic intubation, the drip is either slowed to the expected maintenance rate (40 to 100 drops per minute) or stopped completely in sensitive patients and endotracheal intubation is performed (see page 151). Should apnea (to be distinguished from reflex breath holding, see page 118) develop during or after intubation, the drip is discontinued and controlled respiration is maintained by administering 500 to 800 cc. of gas mixture by intermittent positive pressure 12 to 16 times per minute until spontaneous respiration returns. The drip is restarted at this time at the rate that is expected to give adequate relaxation without apnea. This rate will vary, depending on the size, age, physical condition and plasma cholinesterase activity of the patient, from as little as 5 to 10 drops of an 0.1 per cent solution to as much as 120 drops of an 0.2 per cent solution. If the selected drip rate produces apnea, the drip is immediately discontinued until the return of spontaneous respiratory activity, when it is restarted at a lower rate. Conversely, if the relaxation is inadequate, the drip is speeded up until adequate relaxation is obtained and then it is slowed to a rate somewhat higher than the previous one. It is evident that for the production and maintenance of adequate relaxation, without apnea, it is essential at all times to know the drip rate of the succinylcholine solution and to have a clamp which allows the easy and gradual control of this

rate. Both requirements can be easily met if the anesthetist has at his disposal a stop watch, for the rapid estimation, and a tunnel clamp, for the convenient regulation of the drip rate. Counting 5 drops at rates lower than 90 drops per minute or 10 drops at higher rates allows the estimation of the drip rate in less than 10 seconds. If a tunnel clamp is not available, the use of 2 ordinary screw clamps can be substituted. The drip rate can be adjusted coarsely with the first one and fine adjustment can be made with the second.

It should be emphasized once more that whenever succinylchloline or any other relaxant is used for muscular relaxation the patient's spontaneous respirations must be assisted by gentle pressure on the breathing bag during inspiration. The assistance should be adequate to ensure a tidal volume of 500 to 800 cc. with a minute volume of 6 to 10 liters. The continuous palpation of the breathing bag, necessary for this maneuver, will inform the anesthetist not only of the depth of respiration and the degree of muscular relaxation but, through observation of the rate and rhythm of respiration, will also supply valuable information on the depth of general anesthesia and the presence or absence of disturbing reflexes originating in the operative area.

With this method of succinylcholine administration muscular relaxation can be regulated to the needs of surgery within 30 to 60 seconds and normal respiratory exchange will be re-established within 2 to 3 minutes after discontinuation of the drip. Satisfactory muscular relaxation can be obtained without apnea in patients with normal, decreased, or no plasma cholinesterase activity. The only difference between patients with normal, or no cholinesterase activity will be that the return of normal respiratory exchange might be prolonged by a few

minutes in the latter groups. Consequently, with this method, succinylcholine can be safely used for the production of muscular relaxation in patients with low plasma cholinesterase activity. In fact, since patients with low plasma cholinesterase activity may for other reasons (e.g., dehydration, potassium deficiency, etc.) also be sensitive to long acting relaxants, the production of muscular relaxation with succinylcholine drip increases rather than decreases the patient's safety.

Whenever, because of the requirements of surgery or the inclination of the anesthesiologist, controlled respiration is used with succinylcholine, care must be taken that the plasma level of succinylcholine should be no higher than just adequate to produce apnea. This can be achieved by discontinuing the drip at frequent intervals and observing the time necessary for the return of the first effort of spontaneous respiration. This should occur within 1 to 2 minutes if hypocapnia has not been produced in the patient by excessive controlled respiration. When the time necessary for spontaneous respiration is greater than 1 to 2 minutes the drip rate should be decreased accordingly. For smooth functioning of this method of "back titration," the recommended minute volume of respiratory exchange maintained by controlled respiration is 6 to 10 liters with a respiratory rate of 12 to 16 per minute. The maintenance of controlled respiration with this technique will not prolong unduly the return of adequate spontaneous respiration after discontinuation of the drip.

If adequate respiratory exchange and satisfactory depth of general anesthesia are maintained, the administration of succinylcholine in relaxant doses will cause no marked changes in pulse rate or blood pressure.[151,69] Occasionally in sympathetic hyper-reactors (e.g., patients with essential hypertension or hyperthyroidism) and sometimes in

other patients, if the level of general anesthesia is too light, stimuli arising from the operative area may cause elevation of both the systolic and diastolic blood pressure. The administration of 5 to 10 mg. of hexamethonium, repeated as necessary, will return the blood pressure to near its preoperative level and will also abolish other signs of autonomic hyper-reactivity.

Succinylcholine in single intravenous doses is the agent of choice for the production of muscular relaxation for short procedures: endotracheal intubation, orthopedic manipulations, reduction of fractures or dislocations, pelvic examinations, endoscopies and electroshock therapy. Succinylcholine may be life saving in laryngeal spasm. In this condition one should not hesitate to inject rapidly a deliberate overdose (40 to 100 mg.) to obtain sure and prompt laryngeal relaxation.

Because of its controllability in continuous intravenous drip, succinylcholine is the relaxant of choice for the maintenance of prolonged muscular relaxation. When administered according to the technique recommended, with the exception to its use in intra-ocular surgery[257a] (see page 53) there is no known contraindication to its use. It can be applied safely even in the total absence of plasma cholinesterase activity.

Personal experience with several thousand patients leads the author to conclude that the majority of prolonged *apneas reported after the use of succinylcholine were* probably caused by some technical error in the management of the anesthesia. Because of the relatively frequent occurrence of this almost always avoidable complication it might be worth while to consider in some detail various mechanisms that can lead to the development of prolonged apnea with the use of succinylcholine. Only by the thorough understanding of these mechanisms can

this disturbing complication of succinylcholine administration be eliminated.

SUCCINYLCHOLINE APNEA

Causes. Contrary to the widespread belief that the prolonged apnea is always due to low or absent plasma cholinesterase activity or to some indefinite central action of succinylcholine,[37] there can be little doubt that the apnea caused by succinylcholine can be unduly prolonged by various other factors.[197,7a] Experimental evidence[158] suggests that there is little correlation, in patients with normal cholinesterase activity, between the duration of apnea observed after a measured dose of succinylcholine and the hydrolysis rate of this compound in plasmas obtained from the same patients. It is true that when the plasma cholinesterase activity is markedly decreased (e.g.,

TABLE 16

THE RELATIONSHIPS OF THE ENZYMATIC, ALKALINE AND TOTAL HYDROLYSIS OF ACETYLCHOLINE AND SUCCINYLCHOLINE WITH THE DURATION OF THE SUCCINYLCHOLINE APNEA IN PATIENTS WITH NORMAL AND DECREASED PLASMA CHOLINESTERASE ACTIVITY

	Number	*Hydrolysis Rate of Acetylcholine*			*Hydrolysis Rate of Succinylcholine*			*Duration of Apnea in Seconds**
		T	A	T	E	A	T	
Normal Individuals	29	116.0	7.2	123.2	2.6	2.5	5.1	180 ± 9
Moderate Liver Damage	7	59.0	6.2	65.2	1.4	2.2	3.6	348 ± 34
Severe Liver Damage	11	25.0	7.6	32.6	0.8	2.3	3.1	515 ± 40

* After the intravenous administration of 0.6 mg./kg. of succinylcholine.
E = enzymatic; A = alkaline; T = total.

in patients with severe liver disease), the duration of apnea following the same mg./kg. dose of succinylcholine will be increased and it can be 2 to 3 times as great as in patients with normal plasma cholinesterase activity, but it will never be alarmingly long. The failure of the total absence of plasma cholinesterase activity to cause excessive prolongation of apnea is explained by the fact that in contrast to acetylcholine (where alkaline hydrolysis only amounts to a few per cent of the total hydrolysis rate) the alkaline hydrolysis of succinylcholine is considerable[158] (as much as 50 per cent of the total hydrolysis). Hence provided that there is no acidosis present, alkaline hydrolysis which is the same in patients with high or low plasma cholinesterase will eventually terminate the effect of succinylcholine even in the total absence of plasma cholinesterase (see Table 16). Consequently, no more than a threefold increase can be expected in the time necessary for the breakdown of succinylcholine in the plasma of patients without any cholinesterase activity.

The situation is somewhat different when instead of a single large dose excessive quantities of succinylcholine are administered for prolonged periods in continuous drip. In such cases not only will the hydrolysis of the accumulated succinylcholine take a long time but there is also a possibility for the accumulation of the primary breakdown product, succinylmonocholine. This is especially true in patients in whom, because of pathological changes (e.g., kidney disease, circulatory disease, dehydration, etc.) or the effect of the general anesthesia,[285] urinary excretion is decreased or absent. The accumulated succinylmonocholine will not only inhibit the enzymatic hydrolysis of succinylcholine[373] but will also exert a considerable neuromuscular blocking action of its own.[155]

The role of plasma cholinesterase in the development

of prolonged apnea after the use of succinylcholine can be summarized as follows: (1) After the use of moderate (0.3 to 0.6 mg./kg.) doses of succinylcholine the duration of apnea will be 0 to 240 seconds in patients with normal plasma cholinesterase and will rarely exceed 600 seconds even in the total absence of this enzyme. (2) When much larger (1.0 to 2.0 mg./kg.) single doses are used the duration of apnea can be 10 to 15 minutes in patients with normal plasma cholinesterase and as much as 30 to 45 minutes in its total absence. (3) Irrespective of the plasma cholinesterase activity, adequate muscular relaxation can be provided without the development of apnea by succinylcholine administered in continuous drip. If, however, urinary excretion is decreased or absent, the return of normal tidal volume after discontinuation of the drip may be prolonged, due to the accumulation of succinylmonocholine, in patients who in the course of anesthesia received a total dose of succinylcholine in excess of 8 to 10 mg./kg. (4) When excessive doses of succinylcholine have been administered in continuous drip, to produce apnea necessitating controlled respiration, the return of normal respiratory exchange will be somewhat delayed in patients with normal plasma cholinesterase and markedly but not alarmingly so in patients with little or no plasma cholinesterase. (5) Even when both the plasma cholinesterase activity and urinary output are decreased or absent the administration of relaxant doses of succinylcholine will not produce a prolonged adverse effect on respiration. The administration of excessive doses of succinylcholine over prolonged periods to such patients, however, may result in alarmingly prolonged postoperative apnea.

Besides administering excessive doses of succinylcholine to patients with normal cholinesterase, or normal doses

of succinylcholine to patients with low or absent plasma cholinesterase, prolonged apnea may be produced by various other mechanisms. One of these is hyperventilation of the patient. Hyperventilation can prolong the duration of apnea either by decreasing the blood carbon dioxide tension below the level necessary for the stimulation of the respiratory center or by the exhaustion of the Herring-Breuer reflex.[197] The apnea can also be prolonged by reflex breath holding. This form of apnea can develop in patients with excessive vagus irritability if in the course of the respiratory paralysis produced by an overdose of succinylcholine the level of general anesthesia becomes too light. It need not be emphasized that the depressant action of too deep general anesthesia on the respiratory center, especially when combined with hyperventilation, can also cause prolonged apnea.

Finally it is also conceivable that under pathological circumstances succinylcholine has an altered effect on the endplate. In such cases, instead of a depolarization block of short duration, succinylcholine may cause a prolonged non-depolarization block which is reversible by neostigmine.[189]

Prevention. Based on the understanding of its causative mechanism, the following precautions are recommended for the prevention of prolonged postoperative apnea after the use of succinylcholine. (1) Decrease the possibility of voluntary breath holding by using topical anesthesia on the pharynx, trachea and larynx. (2) Do not administer succinylcholine to patients who are already apneic from the central depressant action of other drugs. (3) Do not use excessive single doses of succinylcholine. (4) If low plasma cholinesterase activity is suspected, administer a small trial dose (5 to 10 mg.), or still better, produce relaxation by the cautious administration of an

0.1 per cent intravenous drip of succinylcholine. (5). When succinylcholine is used for the production of prolonged muscular relaxation, give just enough to obtain the desired effect. Do not abolish spontaneous respiratory activity completely and assist, rather than control, respiration. The degree of muscular relaxation should at all times be adjusted to the needs of surgery. (6) When from individual preference, or necessity, controlled respiration is used, the minimal paralyzing dose of succinylcholine should be employed. This can be ensured by discontinuing the drip temporarily, at frequent intervals, and awaiting the return of the first signs of spontaneous respiration. This will prevent the accumulation of large quantities of unhydrolyzed succinylcholine or succinylmonocholine. With controlled respiration the respiratory rate should be kept between 12 to 16 and the respiratory minute volume between 6 to 10 liters in adults. (7) To avoid reflex breath holding or central respiratory depression, regulate the depth of anesthesia according to the respiratory rate and rhythm and other signs of general anesthesia (e.g., wrinkling of forehead, elevation or depression of pulse rate and blood pressure, etc.). (8) If apnea develops during anesthesia, no more succinylcholine should be administered until the cause of the apnea is diagnosed and dealt with.

Treatment. Whenever apnea develops during the administration of succinylcholine, the first task of the anesthetist is to determine its cause. The management of the correctly diagnosed apnea will differ somewhat during anesthesia and in the postanesthetic period.

Apnea due to an overdose of, or sensitivity to, succinylcholine is recognized by the ease with which the patient's lungs can be inflated and by the good relaxation in the operative area. The only exception is the rare case in

which, concurrent with the apnea, bronchiolar spasm is also present. When apnea is caused by reflex breath holding passive inflation of the lung is difficult, blood pressure and pulse rate are usually elevated, and muscular relaxation is poor. When central depression by a general anesthetist agent is the underlying cause, inflation of the lungs is again difficult and painful stimuli from the operative area will often initiate irregular shallow spontaneous respiration in the poorly relaxed patient. In apnea caused by hypocapnia, relaxation is poor and pulse rate and blood pressure are usually normal or below normal.

When apnea develops during anesthesia because of an excess of succinylcholine, its administration should be temporarily discontinued. On resumption of spontaneous respiration the succinylcholine administration can be recommenced at a lower rate. When the cause of apnea is reflex breath holding, the depth of general anesthesia should be deepened. On occasion, if the patient's slow pulse rate indicates vagus stimulation, supplementary doses of intravenous atropine may be of help. When central depression is responsible for the respiratory arrest, the administration of succinylcholine in the absence of respiratory signs has to be governed by the relaxation of the operative area alone. It need hardly be emphasized that no further doses of drugs capable of causing respiratory depression should be administered under such circumstances until the return of spontaneous respiratory activity. Whatever the cause of the apnea care should be taken to avoid hyperventilation of the patient. Otherwise, because of hypocapnia and exhaustion of the Herring-Breuer reflex, the apnea may persist after the elimination of the original cause. As already suggested, the rate of controlled respiration should not exceed 16 and its volume 6 to 10 liters per minute. If hyperventilation is the original cause of

the apnea, it may be necessary to reduce temporarily the rate and minute volume of controlled respiration to hasten return of spontaneous respiratory activity.

In the immediate postanesthetic period the apnea caused by accumulation of succinylcholine or its primary breakdown product, succinylmonocholine, is best treated, as the circumstances require, by careful controlled or assisted respiration. The administration of plasma cholinesterase concentrates has been suggested[17,132,196] to facilitate the hydrolysis of accumulated succinylcholine. The intravenous injection of relatively large doses of this enzyme, although capable of raising the plasma cholinesterase level in normal individuals, failed to shorten the duration of prolonged postoperative apnea under clinical circumstances.[37] This finding is not at all surprising if one considers that the accumulated succinylmonocholine, little affected by plasma cholinesterase[148] and various other factors can also contribute to prolonged postoperative apnea after succinylcholine. Although on theoretical grounds, the administration of neostigmine should be contraindicated in cases of prolonged succinylcholine apnea because of its inhibitory action on cholinesterases, in fact several cases have been reported in which the administration of this drug was seemingly beneficial.[182,329,196,191] It is possible that in these instances, the endplate became more resistant to depolarization and succinylcholine acted as a non-depolarizing rather than a depolarizing relaxant.[143,368] Neostigmine, by inhibiting cholinesterase, increases the concentration of acetylcholine at the endplate and this increased quantity of acetylcholine is able to displace succinylcholine, depolarize the endplate and thereby re-establish neuromuscular conduction.

When there is reason to believe that the prolonged apnea is caused by accumulation of succinylmonocholine

due to decreased urinary output, a mild osmotic diuretic (e.g., 500 cc. 10 per cent dextrose or 50 to 100 cc. 50 per cent dextrose i.v.) may be useful.

Apnea caused by reflex stimulation from the endotracheal tube can promptly be remedied by its removal. When the origin of the apnea is central depression, caused by excessive doses of intravenous barbiturates or potent analgesics, the intravenous administration of picrotoxin, or metrazol or that of n-allylnormorphine or levallorphan respectively may re-establish spontaneous respiration.

MISCELLANEOUS MUSCLE RELAXANTS

Consideration of the numerous natural and synthetic quaternary ammonium type muscle relaxants is far beyond the scope of this short monograph. Most of these agents have only been tested in laboratory animals and many of them, although of some theoretical interest, possess unwanted side effects that make them unsuitable for clinical application. Two compounds, laudexium and suxethonium, however, have been used in clinical practice and will be discussed briefly.

LAUDEXIUM METHYL SULPHATE *(Laudolissin)*

Laudexium was synthetized by Taylor and Collier[362,363] and its pharmacological properties were investigated by Collier and Macauley.[85] It was studied in unanesthetized human volunteers by Bodman[32,33] and was used in clinical anesthesia by Bodman *et al.*,[34] Binning,[30] Lederman,[256] Dundee *et al.*,[119] Wyant and Sadove[411] and Hunter.[232a]

Laudexium (see structural formula in Figure 1 on page 16 and its physical and chemical properties in Table 2 on page 18) is a non-depolarizing muscle relaxant. In the rabbit and the cat it is more potent and in the rat and the mouse it is less potent than d-tubocurarine. On the sciatic

nerve-tibialis anterior preparation of the cat, it is about 50 per cent longer acting than d-tubocurarine. The neuromuscular effect of laudexium is antagonized by neostigmine and also by small doses of succinylcholine. Ether potentiates the neuromuscular activity of laudexium but it is unaffected by thiopenthal sodium. In cats the autonomic and histamine liberating effect of laudexium is about one sixth to one fourth of that of d-tubocurarine.

In unanesthetized human volunteers,[33] laudexium was about half as potent as d-tubocurarine. 0.15 mg./kg. produced 50 per cent reduction of grip strength; the corresponding value for d-tubocurarine was 0.08 mg./kg. Neostigmine was found to be a less effective antagonist of laudexium than of d-tubocurarine. The intravenous injection of 1.0 mg. of neostigmine 10 minutes before the administration of laudexium decreased its activity by a factor of 1.4; the corresponding value for d-tubocurarine was 1.7. Doses of laudexium smaller than those necessary for 100 per cent depression of the grip strength did not interfere with the maximum inspiratory effort of the volunteers. Laudexium in doses up to 0.24 mg./kg. had no effect on pulse rate or blood pressure. Measured by the intradermal injection of equipotent doses, the histamine releasing effect of laudexium in man was about the same as that of d-tubocurarine.

In anesthetized patients, the mg./kg. dose of laudexium capable of producing adequate muscular relaxation is about double that of d-tubocurarine.[232a] The average initial dose of laudexium is 12 to 40 mg. depending on the age, weight and physical condition of the patient. Following the intravenous injection of the initial dose maximum relaxation develops in 3 to 5 minutes. The relaxation of the laryngeal muscles is less complete than after equivalent doses of d-tubocurarine. The duration of action of the

initial dose is about 30 to 40 minutes. Supplementary doses of one third to one half of the initial dose have an effect of about 60 minutes duration. Subsequent injection of the same fractional dose results in progressive prolongation of action. Its cumulative effect is greater than that of d-tubocurarine.

The neuromuscular effect of laudexium is even more markedly potentiated and prolonged by ether than that of d-tubocurarine.[119] Neostigmine, even in excessive doses (5 mg.), is a less effective antagonist of laudexium than of d-tubocurarine.[232a] Recurarization is more likely to occur after *neostigmine in patients receiving laudexium than in* those to whom d-tubocurarine was administered.[119]

According to Dundee[119] abnormal sensitivity to laudexium was observed in only one out of 524 cases. Nine patients of this same series were resistant to laudexium and required 2 to 3 times the normal average dose for the maintenance of muscular relaxation. All these patients had varying degrees of liver damage and in 5 of them cholinesterase was low.[119]

Laudexium has little or no circulatory effect in man. Likewise, there is rarely any clinical evidence of histamine release.

SUXETHONIUM (Brevedil "E")

Suxethonium is a depolarizing muscle relaxant. It was first synthetized by Bovet and his associates[43] and used clinically by Valdoni in 1949.[378] It differs from succinylcholine by the substitution of an ethyl group in place of a methyl group in both quaternary nitrogens of succinylcholine (see Figure 1 page 17). Its physical and chemical properties are described in Table 2 (page 18).

Its pharmacological action resembles that of succinylcholine very closely. It is hydrolyzed in human plasma

about 50 per cent faster than succinylcholine.[153] On a molar basis it is also about 50 per cent less potent in man than succinylcholine. When 1.2 mg./kg. of suxethonium diiodide are administered intravenously in 30 seconds to anesthetized man apnea develops in about 30 seconds after the end of injection. The average duration of appnea was 76 seconds after this dose. The incidence of muscular twitching with its use is somewhat less than with succinylcholine. Because its duration of action is even shorter than that of succinylcholine it has been recommended for use in electroshock therapy.[125,354]

10

MISCELLANEOUS USES OF MUSCLE RELAXANTS

Muscle relaxants in convulsive shock therapy. The therapeutic use of muscle relaxants: Fields of usefulness; technique of administration of muscle relaxants in neuromuscular disorders; technique of administration of muscle relaxants in tetanus. Diagnostic use of muscle relaxants.

ALTHOUGH at present neuromuscular blocking agents are used primarily for the production of muscular relaxation in anesthetized patients, other medical uses of curare preceded the anesthetic application of muscle relaxants by several decades. Crude curare extracts were used in the second half of the 19th century for the prevention of the convulsions of tetanus[332,388] in status epilepticus,[369] and in chorea.[114] Later West[390,391,392] advocated the use of curare in Parkinsonism, spastic paraplegia and tetanus. The earliest standardized curare preparations were first used for modifying the peripheral effects of shock therapy.[25]

The detailed discussion of the non-anesthetic applications of muscle relaxants is beyond the scope of this monograph. On the other hand, the anesthesiologist is likely to be approached by his colleagues whenever problems arise in connection with the use of neuromuscular blocking agents. Consequently, a brief description of the tech-

niques of the various medical applications of muscle relaxants cannot be omitted.

MUSCLE RELAXANTS IN CONVULSIVE SHOCK THERAPY

The main disadvantages associated with the use of unmodified convulsive shock therapy are: (1) The danger of fractures and dislocations of the bones of the vertebral column and the extremities.[25,214,9] (2) Circulatory changes characterized by marked elevation of the arterial and venous blood pressure, elevation of pulse rate, reduction of pulse pressure, various electrocardiographic signs of pathological irritability of the myocardium and increased vagal tone, not infrequently resulting in cardiac fatalities,[6,207,217] or cerebro-vascular accidents. (3) Anoxic death caused by laryngeal spasm or apnea of central origin.[382] (4) Extreme anxiety of the patient that frequently prevents continuation of the treatment.[355]

Most psychiatrists believe that the therapeutic effect of shock therapy is not diminished if a sleeping dose of a short acting barbiturate is given before the administration of the electric current and the severity of the tonic and clonic convulsions is reduced by muscle relaxants. Experience has demonstrated that the dangers of unmodified shock therapy can be almost completely eliminated by the use of intravenous barbiturates and muscle relaxants.[214,9,216,120,125] The fatalities reported after the use of muscle relaxants in electroshock therapy occurred when long acting relaxants were employed and personnel and equipment necessary for handling respiratory emergencies were not readily at hand.

Since the duration of electrically induced convulsions in shock therapy is brief, the anesthetist should aim at

producing neuromuscular block of short duration but adequate intensity. Of the available muscle relaxants, only succinylcholine and suxethonium are capable of producing profound muscular relaxation the duration of which can be limited to 1 to 3 minutes. Both succinylcholine[216,192] and suxethonium[125,354] have been employed successfully for the modification of the convulsions of electroshock therapy.

Despite the small dose of intravenous barbiturate and the fleeting action of the muscle relaxant recommended, it is absolutely essential that equipment for endotracheal intubation and artificial respiration with oxygen as well as personnel trained in these techniques be constantly available during treatment. Effective, safe and not unpleasant shock therapy necessitates careful team work. The team, depending on the number of cases to be treated at one session should consist of a trained anesthetist and psychiatrist with one experienced nurse in the treatment room. Additional attendants will be required to supervise the patients during recovery. When relatively small numbers of patients are to be treated and time is of secondary importance, a trained anesthetist and a psychiatrist only are required.

The recommended technique is similar to the one described by Steven *et al.*[355] The patients receive 0.4 to 0.6 mg. of atropine sulphate intramuscularly 45 to 60 minutes before the start of therapy. In the treatment room a sleeping dose (4 to 16 cc.) of 2.5 per cent thiopenthal sodium is administered intravenously to the patient. Before the selected dose of succinylcholine is injected in 20 to 30 *seconds (from another syringe but through the same* needle) a rubber oropharyngeal airway, that also substitutes for the customary rubber gag, is inserted. The dose of succinylcholine, depending on the age, weight and

physical condition of the patient, varies between 10 and 50 mg. Larger doses are seldom necessary. Immediately after the injection of succinylcholine the electrodes are applied, the patient's lungs are inflated several times with oxygen, and about 30 to 40 seconds after the end of the succinylcholine injection, the shock is administered. The shock is usually followed by brief and mild contraction of certain muscle groups. Inflation of the lungs with oxygen is continued as soon as possible following the administration of the shock. After cessation of convulsions the patient is turned on his side to allow any accumulated secretion to run out of his mouth and artificial respiration with oxygen is continued until the return of spontaneous respiration: this usually takes place within 1 to 2 minutes. During the recovery period the patient should be observed by a trained attendant.

The use of muscle relaxants in electroshock therapy not only decreases the danger of fractures, dislocations, circulatory complications[207] and laryngeal spasm, but also markedly curtails the contraindications to this useful therapeutic procedure.[402,174,120,247] It must be kept in mind, however, that the administration of a muscle relaxant, and succinylcholine is no exception, needs specialized training and adequate equipment. Without these the immediate mortality caused by asphyxia will be greater with use of muscle relaxants than without them, and anyone who undertakes the use of muscle relaxants under such circumstances subjects his patients to unjustified danger.

THE THERAPEUTIC USE OF MUSCLE RELAXANTS

The physiological basis of the therapeutic application of muscle relaxants is based on two premises: (1) that the curare type drugs are capable of inhibiting neuromuscular transmission to the muscle fibers responsible for muscle

producing neuromuscular block of short duration but adequate intensity. Of the available muscle relaxants, only succinylcholine and suxethonium are capable of producing profound muscular relaxation the duration of which can be limited to 1 to 3 minutes. Both succinylcholine[216,192] and suxethonium[125,354] have been employed successfully for the modification of the convulsions of electroshock therapy.

Despite the small dose of intravenous barbiturate and the fleeting action of the muscle relaxant recommended, it is absolutely essential that equipment for endotracheal intubation and artificial respiration with oxygen as well as personnel trained in these techniques be constantly available during treatment. Effective, safe and not unpleasant shock therapy necessitates careful team work. The team, depending on the number of cases to be treated at one session should consist of a trained anesthetist and psychiatrist with one experienced nurse in the treatment room. Additional attendants will be required to supervise the patients during recovery. When relatively small numbers of patients are to be treated and time is of secondary importance, a trained anesthetist and a psychiatrist only are required.

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desirable. (3) Rigidity and dyskinesias. It is occasionally possible in these conditions to decrease the force and extent of involuntary movements[335] and prepare the ground for physiotherapy. (4) Tetanus where both localized (jaw) or generalized muscle spasms and the clonic convulsions can be controlled by relaxants.

TECHNIQUE OF ADMINISTRATION OF MUSCLE RELAXANTS IN NEUROMUSCULAR DISORDERS

Both aqueous[22,109] and oily solutions[334,80,387] of purified curare extracts and d-tubocurarine have been used for the treatment of various neuromuscular disorders. In chronic neuromuscular conditions where prolonged but not too profound muscular relaxation is desirable, the repository preparations (e.g., Tubadil) have proved to be safe and effective.[169,237,36,212,258] Tubadil contains 25 mg. d-tubocurarine pentahydrate in 1 cc. of a peanut oil-oxycholesterol-beeswax base. It is administered intramuscularly. Intravascular injection should be meticulously avoided. Death has occurred in at least one patient from the accidental intravascular injection of d-tubocurarine suspension (50 mg. in 2 cc.).[310a] It is advisable to warm the depository d-tubocurarine to 100–110° F. and shake the container well before filling the syringe. The dose of repository d-tubocurarine should not exceed 0.5 mg./kg. in outpatients and 1.0 mg./kg. in hospitalized patients. In acute and chronic neuromuscular disorders the patient's sensitivity to d-tubocurarine should be tested by the administration of an 0.2 to 0.3 mg./kg. dose of the repository preparation. This is especially important in poliomyelitis patients. When administered to outpatients, the patient himself, or a responsible companion, should be made familiar with the possible dangerous respiratory

tone and tonic contraction in concentrations which have little effect on neuromuscular transmission associated with voluntary movements; (2) that the transmission of central impulses associated with increased reflex irritability or with dyskinesias (e.g., Parkinsonism or Little's disease) can be blocked at the myoneural junction by concentrations of muscle relaxants that interfere little or not at all with voluntary movements.

Fields of usefulness. From the practical point of view, the conditions in which muscle relaxants may be beneficial can be grouped as follows: (1) Muscle spasm due to trauma, orthopedic deformities, osteoarthritis, periarthritis, myositis, and direct pressure on nerve roots (e.g., ruptured intervertebral disc, malignant growth). Clinical manifestations of muscle spasm are seen in low back pain, torticollis and the shoulder-hand syndrome. In the latter, the circulatory manifestations of reflex sympathetic hyperactivity are usually also present. Frequently the muscle spasm, and the deformity caused by it is a protective *mechanism. When the muscle spasm is the result of direct* pressure on a nerve root (e.g., in ruptured intervertebral disc), pain characterized by segmental distribution will persist after the relief of the generalized muscle spasm and diffuse pain of the involved area. (2) Spasticity caused by spinal cord injury, degenerative central nervous system disease (e.g., multiple sclerosis), Little's disease and poliomyelitis. In most of these conditions the spasticity is due to the abolition of central inhibition caused by the destruction of cortico-spinal pathways or, in poliomyelitis, those of the anterior horn cells. In this group of disorders the role of the muscle relaxant is not only the direct relief of spasticity but also the facilitation of more intensive physiotherapy and rehabilitation.[317] Analgesia, however, should also be provided if the patient's cooperation is

drip than with the slowly acting non-depolarizing drugs. In practice, however, it is evident from the clinical experience obtained in the treatment of tetanus with succinylcholine that the quantity of this agent necessary for the control of spasms almost invariably results in respiratory depression necessitating tracheotomy and assisted or controlled respiration.[409,164] In contradistinction it is possible in some instances to control the hyperspasticity of tetanus with doses of d-tubocurarine that will not necessitate the continuous assistance of respiration. The theoretical advantages of d-tubocurarine in the treatment of tetanus are probably due to the fact that, while small doses of d-tubocurarine may abolish increased muscle tone without total paralysis, subparalyzing doses of depolarizing agents, like succinylcholine, have at first an additive effect to that of tetanic stimuli.[299] Only larger doses of depolarizing drugs which will produce neuromuscular block resulting in marked diminution of respiratory activity are of any value in the treatment of tetanus.

The following course is recommended for the use of muscle relaxants in the treatment of the less severe cases of tetanus: Patients should be kept in a quiet, dimly lighted room. Immediately on admittance an intravenous infusion of 5 per cent dextrose in water is started in a large freely accessible vein with a canula or a plastic catheter, Equipment for endotracheal intubation and artificial respiration with oxygen is kept in readiness. A test dose of 0.1 to 0.15 mg./kg. of a watery solution of d-tubocurarine is administered intravenously followed immediately by the intramuscular injection of 1.0 mg./kg. of a depository d-tubocurarine preparation. At the same time a 1.0 to 1.5 mg./kg. dose of pentobarbital is given intravenously followed by 1.5 to 3.0 mg./kg, of sodium phenobarbital intramuscularly. If the patient develops convulsions be-

effects of d-tubocurarine and be instructed to seek medical help immediately on the first sign of developing respiratory embarrassment. It is advisable to supply outpatients with a few 15 mg. tablets of neostigmine and 0.6 mg. tablets of atropine sulphate and instruct them to take one of each as soon as any respiratory difficulty is observed. The effect of the intramuscular injection of Tubadil is noticeable in 45 to 60 minutes. The full effect, especially after the first injection, may not develop for several hours. The plasma level of d-tubocurarine does not exceed 1 microgram/cc. even when Tubadil is administered in 1 mg./kg. doses.[286] This is in contrast with the 2.8 to 13.0 microgram/cc. of plasma level observed by Pittinger *et al.*[310] after the intravenous administration of aqueous d-tubocurarine in 15 to 30 mg. doses. With the recommended dosage the only side effects seen in about 15 per cent of the cases are diplopia and incoordination of muscles.[258] Respiratory embarrassment is rarely encountered. In chronic cases injections can be repeated at 24 hour intervals. In patients undergoing physiotherapy the repository d-tubocurarine should be injected 2 to 3 hours before the start of treatment.

Technique of the administration of muscular relaxants in tetanus. Curare,[392,100,2,179,82,165] decamethonium,[240] and gallamine[348,378a] in watery solution and d-tubocurarine in oily solution[387,328] have been used for the control of the spasms and convulsions of tetanus. More recently succinylcholine in continuous intravenous drip[409,164] has also been used for this purpose.

The use of both the long acting, non-depolarizing and the short acting depolarizing muscle relaxants have their advantages as well as their disadvantages in the treatment of tetanus. It would appear to be easier to adjust the quantity of relaxant to the rapid variation of the muscle tone that characterizes tetanus[409] with a succinylcholine

spasticity and convulsions is attempted by central depressants alone.[237]

Whether the combination of depository d-tubocurarine and aqueous solutions of this drug, or succinylcholine in continuous drip are employed for the control of the convulsions of tetanus, it is essential that an experienced physician with ample knowledge of the disease, resuscitation and oxygen therapy and the pharmacology of muscle relaxants be at hand constantly in the acute phase of the disease and readily available at all times until the patient is completely out of danger. This requirement is self evident when succinylcholine in continuous drip is used and the speed of the infusion has to be regulated to prevent convulsions on the one hand and respiratory depression on the other. The administration of succinylcholine over several days[409,164] is by no means simple and requires careful consideration of various factors (e.g., the accumulation of succinylmonocholine) which may complicate the pharmacological effects of succinylcholine. The presence of a physician is equally imperative with the use of d-tubocurarine where the occasional administration of small intravenous doses of either d-tubocurarine or edrophonium might be necessary.

The treatment of tetanus, irrespective of the type of muscle relaxant used for the control of convulsions, requires uninterrupted surveillance of the patient. Just as one does not consider leaving a patient receiving muscle relaxant for major surgery unattended, the patient suffering from tetanus should never be left without constant medical supervision.

DIAGNOSTIC USE OF MUSCLE RELAXANTS

Muscle relaxants and their antagonists are useful aids in the diagnosis of myasthenia gravis. Neostigmine,[381] galla-

fore the effect of the depository d-tubocurarine becomes manifest, or if the initial dose fails to control all convulsive seizures, additional small doses (0.04 to 0.1 mg./kg.) of aqueous d-tubocurarine can be administered intravenously. Should the degree of curarization necessary to control convulsions cause temporary respiratory embarrassment, breathing should be assisted with oxygen.

In severe tetanus prophylactic tracheotomy should be performed immediately [378a] and enough muscle relaxant given to control convulsions. This will almost always necessitate the use of artificial respiration, preferably with an alternating positive-negative pressure device. Until the patient becomes gradually accustomed to the respiratory paralysis light anesthesia is maintained by small doses of intravenous barbiturates and a 50-50 per cent mixture of *nitrous oxide-oxygen.*

The tracheotomy not only guarantees a patent airway, but also facilitates the removal of tracheo-bronchial secretions thereby minimizing the danger of respiratory infections and atelectasis. Use of a Levine tube for purpose of gastric feeding is also advisable in these cases.[319a]

By means of the continuously running intravenous infusion, the patient's fluid, electrolyte and vitamin requirements and most of his caloric needs can be supplied. A dependable and rapid route is also available for the administration of sedatives and other drugs as required. If, the activity of the respiratory musculature is seriously depressed by curare, repeated small doses of intravenous edrophonium (5 to 10 mg. or less in children) can be given.

If the patient is kept mildly sedated but conscious, free of convulsions, receives the indicated combination of surgical treatment, antibiotics, antitetanus toxin and necessary supporting therapy, the prognosis of tetanus will be much better than in cases where the control of the

extreme sensitivity towards these drugs and that the same per cent of myasthenics are not abnormally sensitive to non-depolarizing muscle relaxants.[307] The possible dangers involved in administering non-depolarizing neuromuscular blocking agents to myasthenic patients must be fully realized when these tests are performed. Personnel trained in endotracheal intubation and artificial respiration must be readily available with the necessary equipment.

In contrast to the increased sensitivity of myasthenics towards non-depolarizing muscle relaxants they show no such sensitivity toward decamethonium[78,79,307] and other depolarizing relaxants. While the slow intravenous injection of 2.5 mg. of decamethonium invariably causes a marked decrease of the amplitude of the muscle action potential (recorded by electromyography) in normal individuals, the same dose causes little or no decrease and occasionally increases the amplitude of the muscle action potential in myasthenics. Similarly, instead of producing progressive paralysis of the skeletal muscles as in normal individuals small doses of decamethonium may cause temporary remission of signs and symptoms in myasthenics.[307] When larger doses of decamethonium are administered to myasthenics the paralysis first becomes manifest in the involved muscles.[79] Electromyography is essential for the proper evaluation of the decamethonium test in myasthenia gravis. The test consists of the comparison of the electromyogram obtained, through skin electrodes placed on the hypothenar muscles, on percutaneous stimulation of the ulnar nerve before and after the intravenous administration of 2.5 mg. of decamethonium. The absence of a marked decrease in the amplitude of the electromyogram is suggestive of myasthenia. The precautionary measures suggested with the use of curare must also be observed for the decamethonium tests.

mine[115] *and edrophonium*[295] *have all been used for this* purpose.

The physical signs and symptoms related to myasthenia are observed carefully before and at frequent intervals after the administration of neostigmine. Neostigmine methylsulfate may be given intravenously in 0.5 to 1.5 mg. doses (preceded by 0.6 mg. atropine). Special attention is paid to grip strength, vital capacity, and the activity of the muscle groups most involved. Rapid but transient improvement of muscular power after the intravenous administration of neostigmine is diagnostic of myasthenia.

The diagnostic use of edrophonium[295] is based on the same principles as that of neostigmine. The main advantage of edrophonium over neostigmine is the decreased incidence and severity of side effects. Usually 10 mg. of edrophonium are injected intravenously. In contrast to normal individuals in whom this dose usually causes muscular fasciculation, no fasciculations develop in non-treated myasthenics and there is a significant improvement in the activity of the involved muscles.

The diagnostic application of curare and other nondeploring muscle relaxants is based on the markedly increased sensitivity of myasthenics to these compounds. The intravenous injection of 7.5 to 15.0 microgm. of d-tubocurarine chloride per kgm. of body weight[307] (i.e., 0.5 to 1.0 mg. in an average adult), a dose that has no significant effect on normal individuals, causes a marked deterioration in the activity of the involved muscles and may cause the appearance of decreased activity in uninvolved muscles. The intravenous dose of gallamine used for the diagnosis of myasthenia is 0.025 mg./kg.[115] In interpreting the results of diagnostic tests carried out with nondepolarizing muscle relaxants it should be borne in mind that 3 to 4 per cent of non-myasthenic individuals show

sensitivity to succinylcholine and that its response to these agents resembles those of the myasthenic patient. He reported little or no apnea in the newborn after the intravenous administration of succinylcholine in 0.3 to 0.8 mg./kg. doses. Marked respiratory depression, however, was encountered in infants receiving about one third (0.08 mg./kg.) of the adult apneic dose of d-tubocurarine. The studies reported by Stead were carried out, however, on newborn suffering from intestinal obstruction of various etiology and therefore, it is doubtful whether his observations can be applied without reservations to normal infants. Nevertheless, the possibility of increased sensitivity to d-tubocurarine in newborn infants should be kept in mind.

In general the mg./kg. doses of the relaxants recommended for infants and young children by clinicians who prefer controlled respiration are higher than those recommended for adults. Thus, the initial dose of d-tubocurarine suggested varies from 0.3 mg./kg.[89] to 0.4 mg./kg.[7] and the dose of succinylcholine used by the same authors is 1.0 and 2.0 mg./kg. respectively.

Endotracheal intubation of newborn and very young infants with muscle relaxants alone, prior to induction of anesthesia has also been recommended.[106a,288a] Anesthesia is then maintained by the administration of 50-50 nitrous oxide-oxygen or low concentrations of other vapor and controlled respiration.

Recently, McDonald and Bryce-Smith[270a] recommended the intramuscular administration of 2 mg./kg. of succinylcholine with 1 ampule of hyaluronidase or 4 mg./kg. without hyaluronidase to infants and children. Maximum effect is obtained in 2 to 3 minutes with apnea of 6 to 10 minutes and respiratory depression of 10 to 20 minutes duration.

Considering that in the presence of adequate analgesia

11

THE USE OF MUSCLE RELAXANTS IN PATIENTS WITH ALTERED SENSITIVITY

Infancy and childhood. Old age. Myasthenia gravis. Bronchial asthma and other allergic conditions. Cardiovascular disease. Fluid and electrolyte imbalance. Liver disease and decreased plasma cholinesterase activity. Kidney disease.

SURGICAL patients with various pathological conditions may show altered sensitivity to neuromuscular blocking agents. Usually, if increased sensitivity is present, it affects both the non-depolarizing and the depolarizing muscle relaxants. In general old and debilitated individuals may react to normal doses of muscle relaxants with a response of excessive intensity and unusually long duration. In the newborn[353] and in certain pathological conditions, however, increased sensitivity to non-depolarizing muscle relaxants is coupled with a decreased sensitivity towards depolarizing drugs,[78,79] whereas in other disorders the opposite may be true.[117] The following paragraphs describe the use of the muscle relaxants in patients with altered, usually increased, sensitivity to these drugs.

INFANCY AND CHILDHOOD

It has been suggested by Stead[353] that the newborn has an increased sensitivity to d-tubocurarine and a decreased

then can be administered on the basis of the information gained from the intensity and duration of the effects of the initial dose.

Since various degrees of degenerative changes are usually present in the cardiovascular system of the aged, resulting in decreased cardiac reserve, it is important to use a technique of administration that utilizes assisted, rather than controlled, respiration and thereby minimizes the unfavorable circulatory effects of positive pressure breathing.[269]

The aged organism, because of its decreased ability for homeostasis is very sensitive to any deviation from the physiological normal.[140] Consequently, extra care is necessary in assisting the respiration to avoid either carbon dioxide accumulation or hypocapnia. The likelihood of the development of prolonged apnea after sustained controlled respiration is also greater in the aged. This type of apnea may be caused by the interference with the "autorhythmicity" of the respiratory center by the "out of phase" impulses set up by controlled respiration and mediated through the vagi.[113]

With a respiratory rate kept above 12 and a tidal volume supplemented to 500 to 600 cc., carbon dioxide accumulation can be prevented. When the respiratory rate is above 24 it is advisable to assist only with every other spontaneous respiration and thereby prevent the development of hypocapnia.

MYASTHENIA GRAVIS

The markedly increased sensitivity of myasthenic patients to d-tubocurarine was first demonstrated by Bennett and Cash.[24] Dundee[115] subsequently showed that these patients exhibit a similar sensitivity towards gallamine. The sensitivity of myasthenics to non-depolarizing muscle

abdominal relaxation can be produced relatively easily in infants and children, without the necessity for apnea and controlled respiration the use of assisted respiration and smaller doses of relaxants is recommended for this age group. The dose range of muscle relaxants suggested is summarized in Table 17.

TABLE 17

THE MG./KG. DOSES OF MUSCLE RELAXANTS IN INFANTS AND CHILDREN

Relaxant	*Initial Dose*	*Fractional Dose*
d-Tubocurarine*	0.10–0.20	0.05–0.10
Gallamine	1.00–1.50	0.30–0.50
Decamethonium	0.05–0.08	0.02–0.03
Succinylcholine	0.40–0.80	In Continuous Intravenous Drip

* With ether the dose of d-tubocurarine should be reduced to one fifth to one third of the above dose.

In infants to be anesthetized with ether, the intramuscular injection of 0.15 mg./kg. of d-tubocurarine before induction of anesthesia[350] will facilitate the maintenance of good muscular relaxation in lighter planes of general anesthesia without the danger of postoperative respiratory depression.

OLD AGE

The production of muscular relaxation in the aged usually does not present any serious problems. In general, adequate operating conditions can be achieved with smaller mg./kg. doses of relaxants than in young adults of corresponding weight. Even when there is no suspicion of pathologically altered sensitivity to relaxants in the aged, the initial dose of the relaxant should be reduced to two thirds to one half of the adult dose. Fractional doses

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qualitatively similar to the neuromuscular block usually caused by non-depolarizing agents and as such is reversible by neostigmine and edrophonium.[79a]

General anesthesia in myasthenia gravis should preferably be obtained by combinations of nitrous oxide-oxygen, thiopenthal sodium and short acting analgesics. After induction of general anesthesia a test dose consisting of $^1/_{20}$ of the normal dose of d-tubocurarine chloride (0.75 mg. = 0.25 cc.) or gallamine triethiodide (5 mg. = 0.25 cc.) is administered intravenously. If adequate muscular relaxation dose does not develop within 2 to 4 minutes, a similar dose can be administered at 5 minute intervals until the desired effect is obtained. Muscular relaxation, once developed, can be maintained by the repeated administration of a dose equal to the test dose. If the respiratory exchange or the tone of involved muscles is not satisfactory at the termination of anesthesia, edrophonium (10 to 20 mg.) or neostigmine (1.0 to 2.0 mg.) preceded by 0.4 to 0.6 mg. atropine sulfate can be administered. Such patients must be kept under close observation for several hours to avoid the possible dangers of recurarization. As already mentioned, edrophonium and neostigmine can also be used to counteract the neuromuscular effects of depolarizing drugs in myasthenic patients.

BRONCHIAL ASTHMA AND OTHER ALLERGIC CONDITIONS

It is generally agreed that ether is the agent of choice for general anesthesia in the asthmatic patient. Furthermore, it has been suggested (page 66) that non-depolarizing relaxants should preferably be used in conjunction with ether anesthesia. Of the commonly used non-depolarizing relaxants d-tubocurarine and dimethyl tubo-

relaxants can be 10 to 20 times greater than that of normal individuals.[307] It has also been demonstrated that the sensitivity of myasthenic patients to decamethonium[344,116a,77a,78] and to succinylcholine can be markedly decreased. The mechanism of the increased sensitivity of myasthenics to non-depolarizing relaxants and their decreased sensitivity to depolarizing muscle relaxants is not yet clear. It is not inconceivable that it is due to a greater resistance of the endplate to acetylcholine[404,58a] and other depolarizing agents.[143]

From the practical point of view it must be remembered that myasthenics also show increased sensitivity towards the neuromuscular activity of ether. Whenever possible the use of this agent should be avoided in these patients and under no circumstances is it permissible to use ether and d-tubocurarine simultaneously in myasthenic patients.

Despite the abnormally increased sensitivity to non-depolarizing relaxants, when used judiciously, these drugs are safer than the depolarizing drugs in the myasthenic patient. The explanation of this seemingly controversial statement lies in the fact that despite a generally increased tolerance, the sensitivity of involved muscle groups to decamethonium may be increased in myasthenics.[78] Because of the generally increased resistance of the noninvolved myasthenic muscles to depolarizing muscle relaxants the dose of these agents necessary for satisfactory relaxation of the abdominal muscles might cause prolonged paralysis of the involved muscle groups. Should these, as is frequently the case, include the pharyngeal muscles serious post-anesthetic complications might ensue. Consequently, the muscle relaxants of choice in myasthenic patients are the non-depolarizing agents. It is also of great theoretical and clinical importance that the neuromuscular block produced by decamethonium in myasthenics is

striction can also be encountered with other muscle relaxants.

Hypoxia is most likely to occur during intubation, extubation or tracheal suction. Relatively short periods of hypoxia which would have no significance in patients with normal cardiac activity may have very serious consequences in the cardiac patient. The following measures are recommended for the prevention of this serious complication in these patients:

(1) The muscle relaxant of choice should have rapid onset of action, give ideal conditions for endotracheal intubation, have maximum controllability, no prolonged post-anesthetic effect and should have neither ganglion blocking or histamine releasing properties. Of the presently available relaxants, succinylcholine approaches this ideal most closely.

(2) Patients should be hyperventilated with 100 per cent oxygen prior to and immediately after intubation. Endotracheal intubation should be carried out as expeditiously as possible; under no circumstances should the patient be left without oxygen for more than 10 to 20 seconds. If the endotracheal tube is not passed within this time limit, the patient should again be hyperventilated with oxygen before intubation is re-attempted.

(3) The dose of muscle relaxant used should be large enough to prevent the possibility of laryngeal spasm during attempted intubation. If despite all precautions laryngeal spasm develops during intubation or extubation, an adequate dose (30 to 50 mg.) of succinylcholine should immediately be administered intravenously. The laryngeal spasm occurring during extubation at the end of a prolonged surgical procedure can be extremely dangerous especially when it is preceded by prolonged suctioning of the tracheo-bronchial tree. To avoid this complication

curarine are contraindicated in bronchial asthma because of the possibility of histamine release. The likelihood of increased tracheo-bronchial secretions makes the use of benzoquinonium inadvisable in these patients. Consequently, the agent of choice for the production of muscular relaxation in the asthmatic patient is gallamine. The observation that gallamine depresses the irritability of the respiratory tract[224,156] further favors its use. After plane two stage three anesthesia has been induced with ether, 40 to 60 mg. of gallamine are administered intravenously and the patient is intubated. Fractional doses of 10 to 30 mg. of gallamine are then administered as required. Similarly to decrease the possibility of bronchiolar spasm and other allergic manifestations the combined use of ether and gallamine is recommended for the production of muscular relaxation in patients with allergic history.

CARDIOVASCULAR DISEASE

The muscle relaxants, in clinically used doses, have little or no effect on either the contractility or the conductivity of the myocardium. The most important considerations in the use of muscle relaxants in cardiac patients are: (1) ensure adequate oxygenation at all times, and (2) avoid the peripheral circulatory disturbances occasionally caused by the ganglion blocking or histamine releasing properties of certain relaxants, principally those of d-tubocurarine and dimethyl tubocurarine. The patient's oxygenation may become inadequate due to broncho-constriction or inadequate assistance or replacement of his spontaneous respiratory activity. Bronchoconstriction is an infrequent complication of the use of muscle relaxants and, as already mentioned, its incidence is greatest with d-tubocurarine.[255] Occasionally, especially if general anesthesia is maintained by thiopenthal sodium or cyclopropane, bronchiolar con-

muscle relaxants is very variable and cannot be accurately predicted even by the experienced anesthesiologist. The change is usually in the direction of increased sensitivity. Smaller doses of muscle relaxants tend to produce neuromuscular block *of greater intensity and more prolonged* duration. This is especially true when non-depolarizing relaxants are used in patients with potassium deficiency. This increased sensitivity can be explained partly on the basis of the action of the potassium ion at the endplate and partly by the decreased urinary excretion that usually accompanies fluid and electrolyte disturbances in the surgical patient. As already mentioned (see page 55) with the exception of succinylcholine the mechanism primarily responsible for the cessation of action of muscle relaxants is urinary excretion. Kidney function, already decreased in the dehydrated patient, can become completely supressed during anesthesia and surgery and cause undue prolongation of the action of muscle relaxants.

Although, theoretically, patients with potassium deficiency should be less sensitive to depolarizing relaxants (e.g., decamethonium or succinylcholine) *in practice* usually the reverse is true. This finding can be explained by the fact that the termination of the action of decamethonium is also primarily dependent on urinary excretion and that plasma cholinesterase activity, responsible for the detoxification of succinylcholine, is usually also decreased in these patients. The best way to avoid undue paralysis of the respiratory muscles during surgery and in the postoperative period in these patients is to use succinylcholine in continuous drip. With this method the sensitivity of each patient can be "titrated" and undue paralysis avoided.

When long acting muscle relaxants are used in patients with fluid and electrolyte imbalance, depending on the condition of the patient, the initial dose should be reduced

the use of succinylcholine before extubation has been recommended[252] and should be considered in certain cardiac patients.

(4) Prolonged tracheo-bronchial aspiration during anesthesia should be avoided since it may cause hypoxia. In the presence of copious secretions tracheo-bronchial suction should be restricted to a few seconds each time with adequate ventilation of the patient between aspirations.

(5)Because of the unfavorable effect of the positive pressure phase of controlled respiration on venous return and cardiac output in patients with inadequate cardiac reserve[269] assisted instead of controlled respiration should be employed. If controlled respiration is unadvoidable, the positive pressure phase should be kept as brief as possible. The use of respirators, or respiratory assistors which provide negative pressure during exhalation will decrease the unfavorable circulatory effects of controlled respiration in these patients.

(6) Undue elevation of blood pressure, whether due to inadequate carbon dioxide removal or to reflex stimulation of the autonomic nervous system during light anesthesia, should not be tolerated. The latter type of blood pressure rise can be counteracted by the intravenous administration of small doses (5 to 10 mg.) of hexamethonium. Usually one or two 5 mg. doses will return the blood pressure to the preanesthetic level. The use of larger initial doses should be avoided as they might cause a precipitous drop in blood pressure, especially in hypertensive patients.

FLUID AND ELECTROLYTE IMBALANCE

Patients with marked fluid and electrolyte disturbances are notoriously poor operating risks. The response of this group of patients to drugs in general and especially to

endplate and cause re-establishment of the neuromuscular block with resulting respiratory embarassment.

LIVER DISEASE AND DECREASED PLASMA CHOLINESTERASE ACTIVITY

Patients with decreased plasma cholinesterase activity caused by liver disease or other pathological conditions show increased sensitivity to succinylcholine. The increased sensitivity is caused by the slower hydrolysis rate of succinylcholine in the plasma of these patients. The duration of apnea following the intravenous injection of an 0.6 mg./kg. dose of succinylcholine was found to be about four times as long (an average of 580 seconds) in these patients as in healthy individuals.[158] The increased sensitivity of patients with low plasma cholinesterase activity, however, does not contraindicate the use of succinylcholine. In fact, when properly applied it is the relaxant of choice for these patients.

Whenever decreased plasma cholinesterase activity is suspected, succinylcholine should be administered in a slow intravenous infusion of an 0.1 per cent solution. Care must be taken not to allow the neuromuscular block to progress to the point of apnea. Adequate muscular relaxation without apnea can be obtained in these patients with surprisingly small doses of succinylcholine without any undue delay in the return of normal respiratory activity following the discontinuation of the succinylcholine drip.

Patients with liver disease had been reported to exhibit a decreased sensitivity to non-depolarizing muscle relaxants.[117] In clinical practice, however, increased rather than decreased sensitivity to non-depolarizing relaxants is frequently encountered. This increased sensitivity is

to one fourth to one half of the usual dose. If after a suitable waiting period the effect of this dose proves to be inadequate, additional small doses can be given until the required result is obtained. Similar caution is necessary in the administration of fractional doses used for the maintenance of relaxation. In the case of prolonged postoperative respiratory depression with non-depolarizing relaxants the intravenous administration of 0.3 per cent potassium chloride at 60 to 100 drops per minute will occasionally hasten recovery of normal neuromuscular activity, when neostigmine or edrophonium were not completely effective.[152]

Patients with marked fluid and electrolyte disturbances have to be carefully watched postoperatively for signs of "recurarization" even if their respiratory activity seems to be satisfactory at the termination of anesthesia. Theoretically there are at least two mechanisms whereby recurarization can occur in these patients. One is the shift of fluid from the extracellular into the intracellular compartment that may occur in the postoperative period. This shift can produce a relative increase in the concentration of the muscle relaxant at the endplate and cause depression of neuromuscular transmission. The other mechanism depends on the rapid fall of the elevated serum potassium level in the immediate postoperative period. This is most prone to occur in dehydrated patients in whom, because of the depression of urinary excretion during anesthesia, the plasma potassium level may become elevated. Since these patients usually receive generous quantities of intravenous fluids during anesthesia, diuresis, with rapid fall of the elevated plasma potassium level, can occur in the immediate postoperative period. The fall in the plasma potassium level will change the balance between potassium and the non-depolarizing muscle relaxant at the

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SUMMARY OF THE USE OF MUSCLE RELAXANTS IN VARIOUS PROCEDURES

Endotracheal intubation. Endoscopies. Supplementation of regional anesthesia. Treatment of laryngeal spasm. Abdomino-pelvic examinations. Reduction of dislocations and fractures.

ENDOTRACHEAL INTUBATION

When the contemplated surgical procedure does not require prolonged muscular relaxation, the shortest acting muscle relaxants, succinyldicholine[145] or its diethyl derivative, suxethonium, are the agents of choice for producing conditions suitable for endotracheal intubation.

It is suggested that the mouth and pharynx be topically anesthetized with a few cc. of 1 per cent tetracaine or other suitable local anesthetic agent. After the induction of light anesthesia with a short acting barbiturate (e.g., thiopenthal sodium) a dose of succinylcholine not exceeding 0.6 mg./kg. (0.4 mg./kg. will usually suffice for the experienced anesthesiologist) is administered intravenously in 25 to 30 seconds. Because of the slow injection muscular fasciculations will be mild or absent. Relaxation will be complete within 30 seconds of the termination of injection and will last, depending on the dose used and the patient in question, 60 to 240 seconds. While waiting for the development of relaxation the pa-

probably due to the poor physical condition of these patients. It is advisable to proceed just as cautiously with the administration of long acting muscle relaxants as in any other group of debilitated patients.

KIDNEY DISEASE

In patients with kidney disease accompanied by decreased urinary excretion the duration of action of the long acting muscle relaxants which are excreted primarily unchanged will necessarily be prolonged. Relaxation can be maintained by smaller and less frequent doses than in normal individuals. Even so, prolonged postoperative respiratory depression cannot always be avoided. Since succinylcholine is almost completely broken down in the body and the termination of its action is little dependent on urinary excretion, it is the agent of choice in patients with decreased kidney function.

doscopies of the respiratory tract and without some spontaneous respiratory activity satisfactory oxygenation of the patient cannot be maintained by the insufflation of oxygen alone. This goal is most easily obtained with the use of a succinylcholine drip. After induction of anesthesia with an intravenous barbiturate the drip rate can be so adjusted that adequate muscular relaxation without respiratory paralysis is maintained. With the patient inhaling the insufflated oxygen satisfactory oxygenation can be maintained even for relatively prolonged endoscopies without the necessity of interrupting the procedure to artificially ventilate the patient.

For very short procedures a single intravenous 0.3 to 0.6 mg./kg. dose of succinylcholine can be used but the results with this method of administration are less safe and reliable. The same applies to the use of the long acting relaxants in endoscopies. The single dose selected will sometimes fail to produce adequate relaxation and occasionally will cause total respiratory paralysis. Furthermore, the duration of their action will frequently outlast the contemplated procedure and require prolonged postanesthetic observation of the patient. This (see page 85) will be necessary even though the effect of the relaxant is terminated by the use of a suitable antagonist.

The use of muscle relaxants will also facilitate the performance of proctoscopies or sigmoidoscopies under light general anesthesia. Since assisted or controlled respiration is feasible with these procedures, the use of a succinylcholine drip is not as essential as in endoscopic interventions carried out on the respiratory tract.

SUPPLEMENTATION OF REGIONAL ANESTHESIA

The use of muscle relaxants in conjunction with regional anesthesia might become necessary if the relaxation pro-

tient is hyperventilated with 100 per cent oxygen. The cords and the trachea are sprayed with the topical anesthetic under direct vision and an endotracheal tube, lubricated with a water soluble lubricant containing a local anesthetic agent, is introduced. If the patient reacts to the spraying of the cords by attempting to cough an additional small dose of intravenous barbiturate can be administered before intubation. If care is taken to avoid stimulation of the cords or trachea, by moving the tube or the patient's head unnecessarily, spontaneous respiration will be resumed shortly after intubation. Anesthesia is then continued with the selected agent. Transition to ether-oxygen or cyclopropane-oxygen anesthesia can be readily accomplished. Unnecessary movements of the endotracheal tube, despite the topical anesthetization, will frequently cause breath holding and thereby interfere with the smooth conduct of anesthesia.

ENDOSCOPIES

Good relaxation of the voluntary muscles of the jaw, tongue, and pharynx are essential for atraumatic performance of diagnostic or therapeutic laryngoscopy, bronchoscopy and esophagoscopy. Although in many patients these procedures can be carried out under topical anesthesia alone, it is frequently necessary to perform these interventions in the anesthetized patient. Even though the endoscopy is to be performed under general anesthesia with the help of a muscle relaxant topical anethesia of the pharynx and larynx should not be omitted.

The agent and method used should be so selected that their application will result in satisfactory relaxation of the muscle groups involved without causing total paralysis of the respiratory muscles. This is important because efficient artificial respiration is not usually feasible during en-

endotracheal intubation cannot be performed promptly, valuable time should not be wasted and artificial ventilation with an oropharyngeal airway must be promptly instituted.

On rare occasions the laryngeal spasm has a tendency to recur after the effect of the muscle relaxant has worn off. In these cases more prolonged relaxation with a succinylcholine drip is advisable. During relaxation the cords should be visualized, any foreign material capable of initiating the spasm removed and the larynx and pharynx topically anesthetized. Recurrence of the spasm after topical anesthetization of the larynx is unlikely. When instead of succinylcholine long-acting muscle relaxants are used in the treatment of laryngeal spasm, their dose should be as generous as that recommended for succinylcholine. Depending on the weight and physical condition of the patient 15 to 30 mg. of d-tubocurarine, 5 to 10 mg. of dimethyl-tubocurarine, 80 to 160 mg. of gallamine, 15 to 30 mg. of benzoquinonium and 3 to 5 mg. of decamethonium are recommended.

The disadvantages of the long acting relaxants in the treatment of laryngeal spasm are: (1) That even when the recommended massive doses are used the development of maximal relaxation takes one and a half to 4 minutes. This is especially true for benzoquinonium. (2) Controlled or assisted respiration frequently has to be employed for as long as 15 to 40 minutes after the resolution of the spasm. Because of its relatively rapid onset of action gallamine is the long acting relaxant of choice for the treatment of laryngeal spasm.

ABDOMINO-PELVIC EXAMINATIONS

The degree of relaxation of the abdominal wall necessary for bimanual abdomino-pelvic examinations cannot

duced by the regional block is inadequate, or the effect of the regional block wears off before completion of surgery.

The administration of muscle relaxants in conjunction with regional anesthesia is governed by the same principles that apply to their administration in other surgical patients. General anesthesia is induced before the administration of the relaxant and then, if the site and nature of the operative intervention makes it necessary, endotracheal intubation is performed. Otherwise, the selection of the relaxant (see page 65) and the conduct of anesthesia are the same as already described.

TREATMENT OF LARYNGEAL SPASM

The use of a muscle relaxant can be life saving in patients who develop laryngeal spasm during anesthesia or under other circumstances (e.g., hypoparathyroidism, electroshock therapy, severe anaphylactic reactions, etc.). Laryngeal spasm is perhaps the only legitimate indication for the rapid intravenous injection of a deliberate overdose of a muscle relaxant. The shortest acting of the available muscle relaxants, preferably succinylcholine, should be used. The recommended 1 to 1.5 mg./kg. intravenous dose injected rapidly will produce complete laryngeal relaxation with apnea within 30 seconds. Adequate artificial ventilation of the patient is usually possible with the help of an oropharyngeal airway without endotracheal intubation. Whether or not endotracheal intubation is performed after the resolution of the spasm depends primarily on the dexterity of the individual attempting the resuscitation and the circumstances of the case. If the person in charge is capable of performing an endotracheal intubation within seconds after the development of relaxation, this should be done. When, however, because of the anatomy of the patient or insufficient skill of the operator,

EPILOGUE

The introduction of muscle relaxants into clinical practice has been one of the major achievements in the development of anesthesiology in the first half of the twentieth century. With the use of muscle relaxants it became possible to obtain controllable relaxation without undue depression of vital physiologic mechanisms by the excessive use of a single agent and truly "balanced" anesthesia became a practical reality. When correctly used they not only make the surgeon's task easier but also decrease the incidence and severity of operative and postoperative complications.

It should be remembered, however, that the original reason for the introduction of muscle relaxants in anesthesiology was the avoidance of the excessive use of any single agent. Now it seems that the hand of the clock has travelled a full circle and many anesthesiologists practice and advocate the use of muscle relaxants to the point of respiratory paralysis, reverting thereby to the same error that the introduction of muscle relaxants attempted to avoid.

Since it is almost always possible to obtain good relaxation by the carefully regulated administration of muscle relaxants without total paralysis of the respiratory muscles, there is seldom justification for the deliberate production of apnea and the use of controlled, instead of assisted respiration.

The advantages and disadvantages of the total paralysis of the respiratory muscles and the use of assisted versus

always be obtained with the light general anesthesia commonly used for this purpose. The single intravenous injection of 0.3 to 0.6 mg./kg. succinylcholine will in 30 seconds provide excellent relaxation lasting 2 to 4 minutes. In cases of suspected succinylcholine sensitivity (see page 118) smaller single doses should be used or a continuous infusion of 0.1 per cent succinylcholine can be substituted. If the general anesthesia is produced with nitrous oxide-oxygen this procedure can be safely used in ambulatory patients.

REDUCTION OF DISLOCATIONS AND FRACTURES

Reduction of dislocations and fractures can be carried out under light general anesthesia induced with nitrous oxide-oxygen supplemented, when necessary, with a short acting analgesic (e.g., alphaprodine) and the intravenous injection of 0.3 to 0.6 mg./kg. succinylcholine injected in 30 seconds. When the contemplated procedure is expected to last longer than 2 to 3 minutes, the single intravenous injection can be replaced by a continuous intravenous infusion of 0.1 to 0.2 per cent succinylcholine solution administered at a rate that will produce the desired muscular relaxation without respiratory arrest.

The second disadvantage of succinylcholine is that its primary breakdown product, succinylmonocholine, also has some neuromuscular activity and therefore in certain circumstances the return of normal respiratory activity may be delayed after its use. For these reasons, if one may hazard a glance into the future, the search for other muscle relaxants will undoubtedly continue. The goal of this search will be to find a non-depolarizing muscle relaxant which will be as short acting and controllable as succinylcholine, its fate in the organism being little affected by pathological changes, its breakdown products having no neuromuscular blocking effect and which will be easily reversible by a harmless antagonist, in the rare instances, when an atypical response will make this necessary.

controlled respiration have been discussed at considerable length in the preceding chapters. It should be emphasized once more, however, that the only sure way to prevent prolonged postoperative apnea when using muscle relaxants is to avoid total respiratory paralysis during surgery and to correct it immediately should it occur. If spontaneous respiratory activity is not completely abolished, the respiratory tidal volume will usually be a reliable guide to the degree of muscular relaxation and the depth of general anesthesia can be estimated from the respiratory rate and rhythm. Or in other words, the maintenance of some degree of spontaneous respiratory activity and the use of assisted respiration make it possible to carry the patient in the optimal plane of general anesthesia and to avoid the dangers of excessive or inadequate depression of the central nervous system and other vital mechanisms.

With the correct use of muscle relaxants, especially that of succinylcholine, prolonged postoperative respiratory depression should be seldom encountered. If despite all precautions the patient's tidal volume is inadequate at the termination of surgery, it is by far the safest to assist the patient's respiration with oxygen until the return of satisfactory spontaneous respiration. The indiscriminate routine use of the antagonists of the long acting relaxants is not without its dangers.

There can be little doubt that of the presently available muscle relaxants, with the exception of very few situations, succinylcholine is the first choice for the production of muscular relaxation. It is also evident that in at least two respects succinylcholine falls short of the pharmacological ideal of the perfect relaxant. One of these is that the block produced by succinylcholine is a depolarization block and therefore, the neuromuscular junction is not in its physiological resting state while under its influence.

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SUBJECT INDEX

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MUSCLE RELAXANTS
in Anesthesiology

By
FRANCIS F. FOLDES, M.D.

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